

EXHIBIT 1



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(54) **BIODEGRADABLE LIPIDS FOR THE DELIVERY OF ACTIVE AGENTS**

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See application file for complete search history.

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(57)

ABSTRACT

The present invention relates to a cationic lipid having one or more biodegradable groups located in a lipidic moiety (e.g., a hydrophobic chain) of the cationic lipid. These cationic lipids may be incorporated into a lipid particle for delivering an active agent, such as a nucleic acid. The invention also relates to lipid particles comprising a neutral lipid, a lipid capable of reducing aggregation, a cationic lipid of the present invention, and optionally, a sterol. The lipid particle may further include a therapeutic agent such as a nucleic acid.

28 Claims, No Drawings

Specification includes a Sequence Listing.

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Related U.S. Application Data

continuation of application No. 14/677,801, filed on Apr. 2, 2015, now Pat. No. 10,369,226, which is a continuation of application No. 13/708,383, filed on Dec. 7, 2012, now Pat. No. 9,061,063.

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BIODEGRADABLE LIPIDS FOR THE DELIVERY OF ACTIVE AGENTS

This application is a continuation of U.S. patent application Ser. No. 16/520,183, filed Jul. 23, 2019, which is a continuation of U.S. patent application Ser. No. 14/677,801, filed Apr. 2, 2015, now U.S. Pat. No. 10,369,226, which is a continuation of U.S. patent application Ser. No. 13/708,383, filed Dec. 7, 2012, now U.S. Pat. No. 9,061,063, which claims the benefit of U.S. Provisional Application No. 61/568,133, filed Dec. 7, 2011, and U.S. Provisional Application No. 61/623,274, filed Apr. 12, 2012, each of which is hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to biodegradable lipids and to their use for the delivery of active agents such as nucleic acids.

BACKGROUND

Therapeutic nucleic acids include, e.g., small interfering RNA (siRNA), micro RNA (miRNA), antisense oligonucleotides, ribozymes, plasmids, immune stimulating nucleic acids, antisense, antagomir, antimir, microRNA mimic, supermir, U1 adaptor, and aptamer. In the case of siRNA or miRNA, these nucleic acids can down-regulate intracellular levels of specific proteins through a process termed RNA interference (RNAi). The therapeutic applications of RNAi are extremely broad, since siRNA and miRNA constructs can be synthesized with any nucleotide sequence directed against a target protein. To date, siRNA constructs have shown the ability to specifically down-regulate target proteins in both in vitro and in vivo models. In addition, siRNA constructs are currently being evaluated in clinical studies.

However, two problems currently faced by siRNA or miRNA constructs are, first, their susceptibility to nuclease digestion in plasma and, second, their limited ability to gain access to the intracellular compartment where they can bind the protein RISC when administered systemically as the free siRNA or miRNA. Lipid nanoparticles formed from cationic lipids with other lipid components, such as cholesterol and PEG lipids, and oligonucleotides (such as siRNA and miRNA) have been used to facilitate the cellular uptake of the oligonucleotides.

There remains a need for improved cationic lipids and lipid nanoparticles for the delivery of oligonucleotides. Preferably, these lipid nanoparticles would provide high drug:lipid ratios, protect the nucleic acid from degradation and clearance in serum, be suitable for systemic delivery, and provide intracellular delivery of the nucleic acid. In addition, these lipid-nucleic acid particles should be well-tolerated and provide an adequate therapeutic index, such that patient treatment at an effective dose of the nucleic acid is not associated with significant toxicity and/or risk to the patient.

SUMMARY

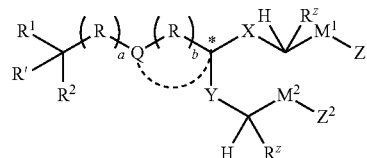
The present invention relates to a cationic lipid and PEG lipid suitable for forming nucleic acid-lipid particles. Each of the cationic and PEG lipids of the present invention includes one or more biodegradable groups. The biodegradable groups are located in a lipidic moiety (e.g., a hydrophobic chain) of the cationic or PEG lipid. These cationic and PEG lipids may be incorporated into a lipid particle for

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delivering an active agent, such as a nucleic acid (e.g., an siRNA). The incorporation of the biodegradable group(s) into the lipid results in faster metabolism and removal of the lipid from the body following delivery of the active agent to a target area. As a result, these lipids have lower toxicity than similar lipids without the biodegradable groups.

In one embodiment, the cationic lipid is a compound of formula (I), which has a branched alkyl at the alpha position adjacent to the biodegradable group (between the biodegradable group and the tertiary carbon):

Formula (I)



or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

- R¹ is absent, hydrogen, or alkyl (e.g., C₁-C₄ alkyl);
- with respect to R¹ and R²,
- (i) R¹ and R² are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkylalkyl, heterocycle, or R¹⁰;
- (ii) R¹ and R², together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclic ring; or
- (iii) one of R¹ and R² is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle, and the other forms a 4-10 member heterocyclic ring or heteroaryl (e.g., a 6-member ring) with (a) the adjacent nitrogen atom and (b) the (R)_a group adjacent to the nitrogen atom;

each occurrence of R is, independently, —(CR³R⁴)—;

each occurrence of R³ and R⁴ are, independently, H, halogen, OH, alkyl, alkoxy, —NH₂, R¹⁰, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R³ and R⁴ are, independently H or C₁-C₄ alkyl);

each occurrence of R¹⁰ is independently selected from PEG and polymers based on poly(oxazoline), poly(ethylene oxide), poly(vinyl alcohol), poly(glycerol), poly(N-vinylpyrrolidone), poly[N-(2-hydroxypropyl)methacrylamide] and poly(amino acids), wherein (i) the PEG or polymer is linear or branched, (ii) the PEG or polymer is polymerized by n subunits, (iii) n is a number-averaged degree of polymerization between 10 and 200 units, and (iv) wherein the compound of formula has at most two R¹⁰ groups (preferably at most one R¹⁰ group);

the dashed line to Q is absent or a bond;

when the dashed line to Q is absent then Q is absent or is —O—, —NH—, —S—, —C(O)—, —C(O)O—, —OC(O)—, —C(O)N(R⁴)—, —N(R⁵)C(O)—, —S—, —S—, —OC(O)O—, —O—N=C(R⁵)—, —C(R⁵)=N—O—, —OC(O)N(R⁵)—, —N(R⁵)C(O)N(R⁵)—, —N(R⁵)C(O)O—, —C(O)S—, —C(S)O— or —C(R⁵)=N—O—C(O)—; or

when the dashed line to Q is a bond then (i) b is 0 and (ii) Q and the tertiary carbon adjacent to it (C*) form a substituted or unsubstituted, mono- or bi-cyclic heterocyclic group having from 5 to 10 ring atoms (e.g., the heteroatoms in the heterocyclic group are selected from O and S, preferably O);

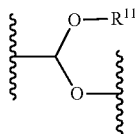
each occurrence of R⁵ is, independently, H or alkyl (e.g. C₁-C₄ alkyl);

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X and Y are each, independently, alkylene or alkenylene (e.g., C₄ to C₂₀ alkylene or C₄ to C₂₀ alkenylene);

M¹ and M² are each, independently, a biodegradable group (e.g., —OC(O)—, —C(O)O—, —SC(O)—, —C(O)S—, —OC(S)—, —C(S)O—, —S—S—, —C(R⁵)=N—, —N=C(R⁵)—, —C(R⁵)=N—O—, —O—N=C(R⁵)—, —C(O)(NR⁵)—, —N(R⁵)C(O)—, —C(S)(NR⁵)—, —N(R⁵)C(O)—, —N(R⁵)C(O)N(R⁵)—, —OC(O)O—, —OSi(R⁵)₂O—, —C(O)(CR³R⁴)C(O)O—, —OC(O)(CR³R⁴)C(O)—, or



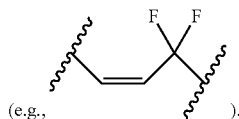
(wherein R¹¹ is a C₂-C₈ alkyl or alkenyl);

each occurrence of R² is, independently, C₁-C₈ alkyl (e.g., methyl, ethyl, isopropyl, n-butyl, n-pentyl, or n-hexyl);

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3; and

Z¹ and Z² are each, independently, C₈-C₁₄ alkyl or C₈-C₁₄ alkenyl, wherein the alkenyl group may optionally be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of Z¹ or Z²



The R¹R²N—(R)_a—Q—(R)_b— group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, R¹R²N—(R)_a—Q—(R)_b— is (CH₃)₂N—(CH₂)₃—C(O)O—, (CH₃)₂N—(CH₂)₂—NH—C(O)O—, (CH₃)₂N—(CH₂)₂—OC(O)—NH—, or (CH₃)₂N—(CH₂)₃—C(CH₃)=N—O—.

In one embodiment, R¹ and R² are both alkyl (e.g., methyl).

In a further embodiment, a is 3. In another embodiment, b is 0.

In a further embodiment, a is 3, b is 0 and R is —CH₂—.

In yet a further embodiment, a is 3, b is 0, R is —CH₂— and Q is —C(O)O—. In another embodiment, R¹ and R² are methyl, a is 3, b is 0, R is —CH₂— and Q is —C(O)O—.

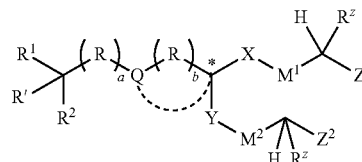
In another embodiment, X and Y are each, independently —(CH₂)_n— wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are —(CH₂)₆—. In another embodiment, X and Y are —(CH₂)₇—. In yet another embodiment, X and Y are —(CH₂)₉—. In yet another embodiment, X and Y are —(CH₂)₈—.

In further embodiments, M¹ and M² are each, independently, —OC(O)— or —C(O)O—. For example, in one embodiment, M¹ and M² are each —C(O)O—.

In another embodiment, the cationic lipid is a compound of formula (II), which has a branched alkyl at the alpha position adjacent to the biodegradable group (between the biodegradable group and the terminus of the tail, i.e., Z¹ or Z²);

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Formula (II)



or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R¹ is absent, hydrogen, or alkyl (e.g., C₁-C₄ alkyl); with respect to R¹ and R²,

(i) R¹ and R² are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkylalkyl, heterocycle, or R¹⁰;

(ii) R¹ and R², together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclic ring; or

(iii) one of R¹ and R² is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle, and the other forms a 4-10 member heterocyclic ring or heteroaryl (e.g., a 6-member ring) with (a) the adjacent nitrogen atom and (b) the (R)_a group adjacent to the nitrogen atom;

each occurrence of R is, independently, —(CR³R⁴)—;

each occurrence of R³ and R⁴ are, independently H, halogen, OH, alkyl, alkoxy, —NH₂, R¹⁰, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R³ and R⁴ are, independently H or C₁-C₄ alkyl);

each occurrence of R¹⁰ is independently selected from PEG and polymers based on poly(oxazoline), poly(ethylene oxide), poly(vinyl alcohol), poly(glycerol), poly(N-vinylpyrrolidone), poly[N-(2-hydroxypropyl)methacrylamide] and poly(amino acid)s, wherein (i) the PEG or polymer is linear or branched, (ii) the PEG or polymer is polymerized by n subunits, (iii) n is a number-averaged degree of polymerization between 10 and 200 units, and (iv) wherein the compound of formula has at most two R¹⁰ groups (preferably at most one R¹⁰ group);

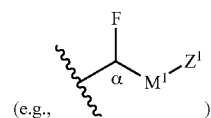
the dashed line to Q is absent or a bond;

when the dashed line to Q is absent then Q is absent or is —O—, —NH—, —S—, —C(O)—, —C(O)O—, —OC(O)—, —C(O)N(R⁴)—, —N(R⁵)C(O)—, —S—S—, —OC(O)O—, —O—N=C(R⁵)—, —C(R⁵)=N—O—, —OC(O)N(R⁵)—, —N(R⁵)C(O)N(R⁵)—, —N(R⁵)C(O)O—, —C(O)S—, —C(S)O— or —C(R⁵)=N—O—C(O)—; or

when the dashed line to Q is a bond then (i) b is 0 and (ii) Q and the tertiary carbon adjacent to it (C*) form a substituted or unsubstituted, mono- or bi-cyclic heterocyclic group having from 5 to 10 ring atoms (e.g., the heteroatoms in the heterocyclic group are selected from O and S, preferably O);

each occurrence of R⁵ is, independently, H or alkyl;

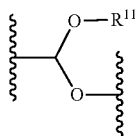
X and Y are each, independently, alkylene (e.g., C₆-C₈ alkylene) or alkenylene, wherein the alkylene or alkenylene group is optionally substituted with one or two fluorine atoms at the alpha position to the M¹ or M² group



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M^1 and M^2 are each, independently, a biodegradable group (e.g., $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(\text{O})\text{S}-$, $-\text{OC}(\text{S})-$, $-\text{C}(\text{S})\text{O}-$, $-\text{S}-$, $-\text{C}(\text{R}^5)=\text{N}-$, $-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^5)=\text{N}-\text{O}-$, $-\text{O}-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{O})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{C}(\text{S})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{N}(\text{R}^5)-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{OSi}(\text{R}^5)_2\text{O}-$, $-\text{C}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})-$, or



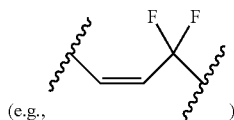
(wherein R^{11} is a C_2 - C_8 alkyl or alkenyl);

each occurrence of R^z is, independently, C_1 - C_8 alkyl (e.g., methyl, ethyl, isopropyl);

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3; and

Z^1 and Z^2 are each, independently, C_8 - C_{14} alkyl or C_8 - C_{14} alkenyl, wherein (i) the alkenyl group may optionally be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of Z^1 or Z^2

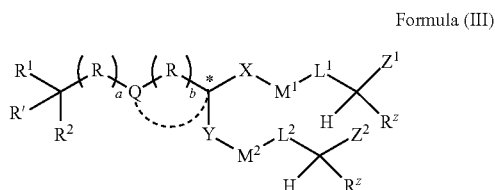


and (ii) the terminus of at least one of Z^1 and Z^2 is separated from the group M^1 or M^2 by at least 8 carbon atoms.

In another embodiment, X and Y are each, independently, $-(\text{CH}_2)_n-$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(\text{CH}_2)_6-$. In another embodiment, X and Y are $-(\text{CH}_2)_7-$. In yet another embodiment, X and Y are $-(\text{CH}_2)_9-$. In yet another embodiment, X and Y are $-(\text{CH}_2)_8-$.

The $\text{R}^1\text{R}^2\text{N}-(\text{R})_a-\text{Q}-(\text{R})_b-$ group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, $\text{R}^1\text{R}^2\text{N}-(\text{R})_a-\text{Q}-(\text{R})_b-$ is $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_3-\text{C}(\text{O})\text{O}-$, $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_2-\text{NH}-\text{C}(\text{O})\text{O}-$, $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_2-\text{OC}(\text{O})-\text{NH}-$, or $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_3-\text{C}(\text{CH}_3)=\text{N}-\text{O}-$.

In another embodiment, the cationic lipid is a compound of formula (III), which has a branching point at a position that is 2-6 carbon atoms (i.e., at the beta (β), gamma (γ), delta (δ), epsilon (ϵ) or zeta position (ζ)) adjacent to the biodegradable group (between the biodegradable group and the terminus of the tail, i.e., Z^1 or Z^2):



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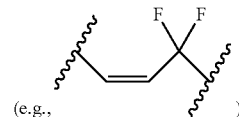
or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R^1 , R^2 , R , R^3 , R^4 , R^{10} , Q , R^5 , M^1 , M^2 , R^z , a , and b are defined as in formula (I);

L^1 and L^2 are each, independently, C_1 - C_5 alkylene or C_2 - C_5 alkenylene;

X and Y are each, independently, alkylene (e.g., C_4 to C_{20} alkylene or C_6 - C_8 alkylene) or alkenylene (e.g., C_4 to C_{20} alkenylene); and

Z^1 and Z^2 are each, independently, C_8 - C_{14} alkyl or C_8 - C_{14} alkenyl, wherein the alkenyl group may optionally be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of Z^1 or Z^2



and with the proviso that the terminus of at least one of Z^1 and Z^2 is separated from the group M^1 or M^2 by at least 8 carbon atoms.

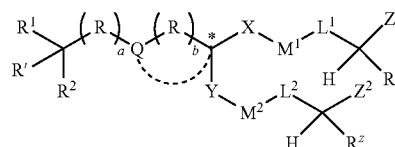
In one embodiment, L^1 and L^2 are each $-\text{CH}_2-$. In another embodiment, L^1 and L^2 are each $-(\text{CH}_2)_2-$. In one embodiment, L^1 and L^2 are each $-(\text{CH}_2)_3-$. In yet another embodiment, L^1 and L^2 are each $-(\text{CH}_2)_4-$. In yet another embodiment, L^1 and L^2 are each $-(\text{CH}_2)_5-$. In yet another embodiment, L^1 and L^2 are each $-\text{CH}_2-\text{CH}=\text{CH}-$. In a preferred embodiment, L^1 and L^2 are each $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$.

In one embodiment, X and Y are each, independently, $-(\text{CH}_2)_n$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(\text{CH}_2)_7-$. In another exemplary embodiment, X and Y are $-(\text{CH}_2)_8-$. In yet another exemplary embodiment, X and Y are $-(\text{CH}_2)_9-$.

The $\text{R}^1\text{R}^2\text{N}-(\text{R})_a-\text{Q}-(\text{R})_b-$ group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, $\text{R}^1\text{R}^2\text{N}-(\text{R})_a-\text{Q}-(\text{R})_b-$ is $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_3-\text{C}(\text{O})\text{O}-$, $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_2-\text{NH}-\text{C}(\text{O})\text{O}-$, $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_2-\text{OC}(\text{O})-\text{NH}-$, or $(\text{CH}_3)_2\text{N}-(\text{CH}_2)_3-\text{C}(\text{CH}_3)=\text{N}-\text{O}-$.

In another embodiment, the cationic lipid is a compound of formula (IIIA), which has a branching point at a position that is 2-6 carbon atoms (i.e., at the beta (β), gamma (γ), delta (δ), epsilon (ϵ) or zeta position (ζ)) from the biodegradable groups M^1 and M^2 (i.e., between the biodegradable group and the terminus of the tail, i.e., Z^1 or Z^2):

Formula (IIIA)



or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

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R¹, R², R, R³, R⁴, R¹⁰, Q, R⁵, M¹, M², a, and b are defined as in formula (I);

each R^z is, independently, C₁-C₈ alkyl (e.g., C₃-C₆ alkyl or C₂-C₃ alkyl);

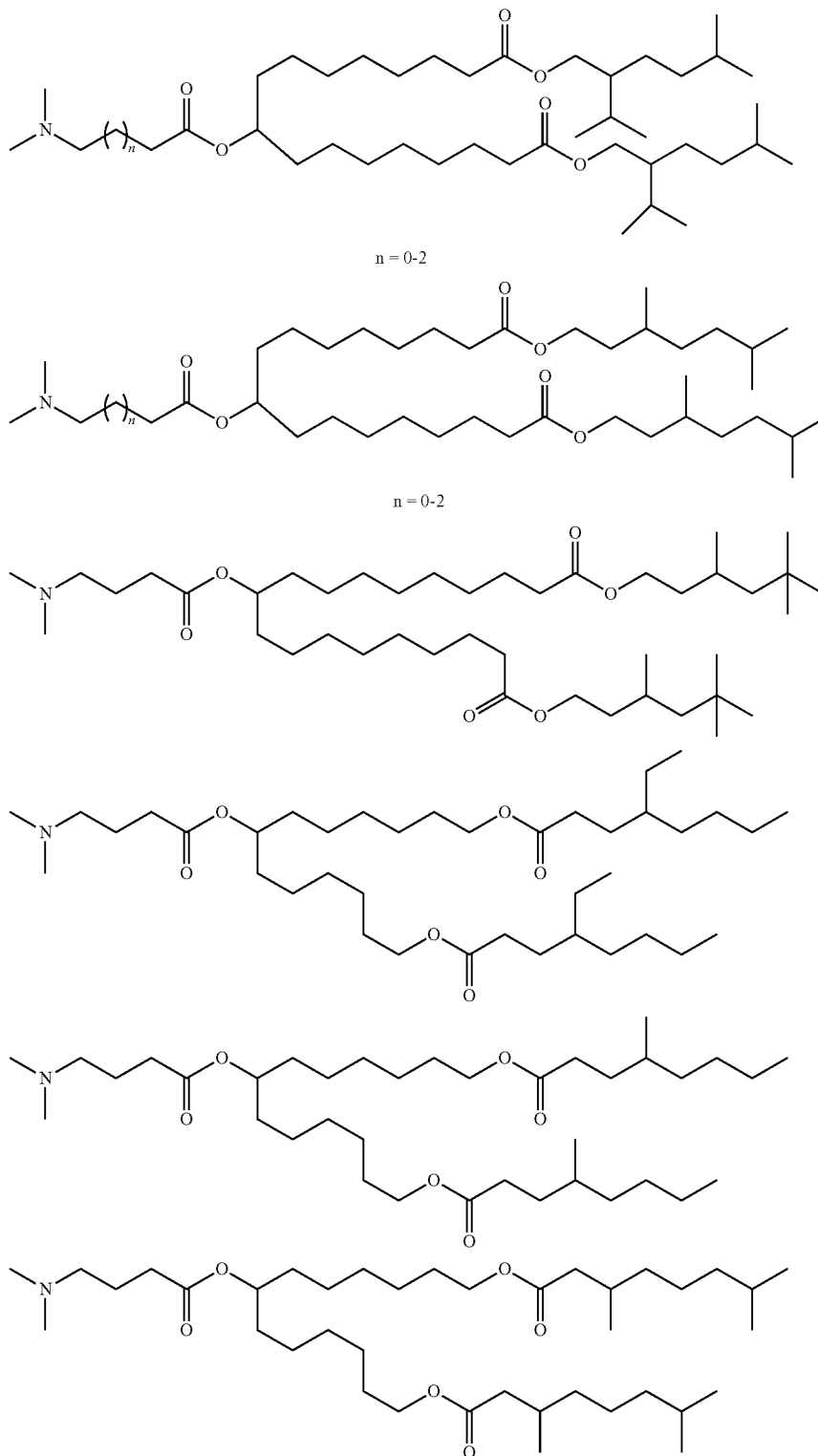
L¹ and L² are each, independently, C₁-C₅ alkylene (e.g., C₂-C₃ alkylene) or C₂-C₅ alkenylene;

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X and Y are each, independently, alkylene (e.g., C₄ to C₂₀ alkylene or C₇-C₉ alkylene) or alkenylene (e.g., C₄ to C₂₀ alkenylene or C₇-C₉ alkenylene); and

Z¹ and Z² are each, independently, C₁-C₈ alkyl (e.g., C₁-C₆ alkyl, such as C₁, C₃ or C₅ alkyl) or C₂-C₈ alkenyl (such as C₂-C₆ alkenyl);

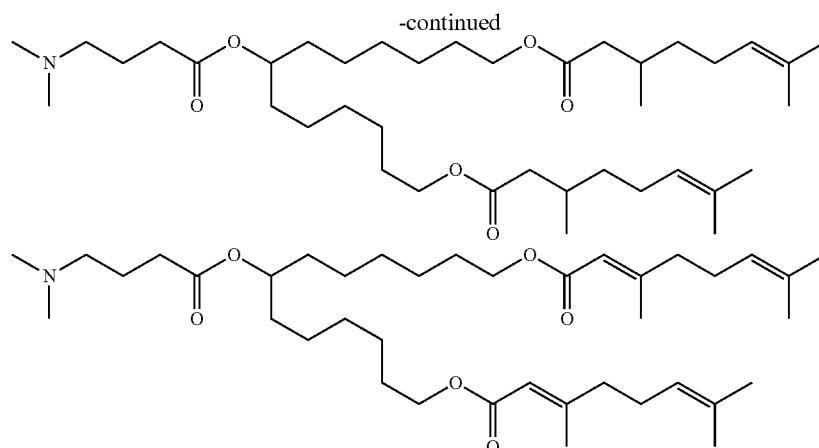
wherein said cationic lipid is not one selected from:



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In one embodiment, L^1 and L^2 are each $-(CH_2)_2-$. In another embodiment, L^1 and L^2 are each $-(CH_2)_3-$.

In one embodiment, X and Y are each, independently $-(CH_2)_n$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, 4 to 12 or 7-9. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(CH_2)_7-$. In yet another exemplary embodiment, X and Y are $-(CH_2)_9-$.

In one preferred embodiment, M^1 and M^2 are $-C(O)O-$ (where the carbonyl group in M^1 and M^2 is bound to the variable X, and the oxygen atom in M^1 and M^2 is bound to the variable L^1 and L^2).

The $R^1R^2N-(R)_a-Q-(R)_b-$ group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, $R^1R^2N-(R)_a-Q-(R)_b-$ is $(CH_3)_2N-(CH_2)_3-C(O)O-$, $(CH_3)_2N-(CH_2)_2-NH-C(O)O-$, $(CH_3)_2N-(CH_2)_2-OC(O)-NH-$, or $(CH_3)_2N-(CH_2)_3-C(CH_3)=N-O-$.

In one preferred embodiment, Z^1 and Z^2 are branched alkyl or branched alkenyl groups.

In one embodiment of formula (IIIA), Z^1 , Z^2 , and each R^z are C_3 - C_8 alkyl (such as a C_3 - C_6 alkyl). In another embodiment of formula (IIIA), Z^1 , Z^2 , and each R^z are C_3 - C_8 branched alkyl (such as a C_3 - C_6 branched alkyl). In yet another embodiment of formula (IIIA), Z^1 , Z^2 , and each R^z are C_3 - C_8 straight alkyl (such as a C_3 - C_6 straight alkyl).

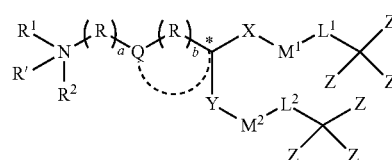
In one embodiment of formula (IIIA), the branching point is at the second position (the β -position) from the biodegradable groups M^1 and M^2 in each tail. Z^1 , Z^2 , and each R^z can be C_3 - C_8 alkyl (e.g., a C_3 - C_6 alkyl), such as a C_3 - C_8 branched alkyl (e.g., a C_3 - C_6 branched alkyl) or a C_3 - C_8 straight alkyl (e.g., a C_3 - C_6 straight alkyl). In one preferred embodiment, M^1 and M^2 are $-C(O)O-$ (where the carbonyl group in M^1 and M^2 is bound to the variable X, and the oxygen atom in M^1 and M^2 is bound to the variable L^1 and/or L^2).

In one embodiment of formula (IIIA), the branching point is at the third position (the γ -position) from the biodegradable groups M^1 and M^2 in each tail. Z^1 , Z^2 , and each R^z can be C_3 - C_8 alkyl (e.g., a C_3 - C_6 alkyl), such as a C_3 - C_8 branched alkyl (e.g., a C_3 - C_6 branched alkyl) or a C_3 - C_8 straight alkyl (e.g., a C_3 - C_6 straight alkyl). In one preferred embodiment, M^1 and M^2 are $-C(O)O-$ (where the carbonyl group in M^1 and M^2 is bound to the variable X, and the oxygen atom in M^1 and M^2 is bound to the variable L^1 and/or L^2).

In one embodiment of formula (IIIA), the branching point is at the third position (the γ -position) from the biodegradable groups M^1 and M^2 in each tail.

In another embodiment of formula (IIIA), M^1 and/or M^2 are not $-O(C(O)-$ (where the oxygen atom in M^1 and/or M^2 is bound to the variable X, and the carbonyl in M^1 and/or M^2 is bound to the variable L^1 and/or L^2). In yet another embodiment of formula (IIIA), Z^1 , Z^2 , and R^z are not C_3 - C_{10} cycloalkyl(C_1 - C_6 alkyl).

In another embodiment, the cationic lipid is a compound of formula (IV), which has a branching point at a position that is 2-6 carbon atoms (i.e., at beta (β), gamma (γ), delta (δ), epsilon (ϵ) or zeta position(ζ)) adjacent to the biodegradable group (between the biodegradable group and the terminus of the tail, i.e., Z^1 or Z^2):



or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R^1 , R^2 , R , R^3 , R^4 , R^{10} , Q , R^5 , M^1 , M^2 , a , and b are defined as in formula (I);

L^1 and L^2 are each, independently, C_1 - C_5 alkylene or C_2 - C_5 alkenylene;

X and Y are each, independently, alkylene or alkenylene (e.g., C_{12} - C_{20} alkylene or C_{12} - C_{20} alkenylene); and each occurrence of Z is independently C_1 - C_4 alkyl (preferably, methyl).

For example, in one embodiment, $-L^1-C(Z)_3$ is $-CH_2C(CH_3)_3$. In another embodiment, $-L^1-C(Z)_3$ is $-CH_2CH_2C(CH_3)_3$.

In one embodiment, the total carbon atom content of each tail (e.g., $-X-M^1-L^1-C(Z)_3$ or $-Y-M^2-L^2-C(Z)_3$) is from about 17 to about 26. For example, the total carbon atom content can be from about 19 to about 26 or from about 21 to about 26.

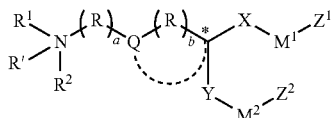
In another embodiment, X and Y are each, independently $-(CH_2)_n$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(CH_2)_6-$. In

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another embodiment, X and Y are $-(CH_2)_7-$. In yet another embodiment, X and Y are $-(CH_2)_9-$. In yet another embodiment, X and Y are $-(CH_2)_8-$.

In one embodiment, the cationic lipid is a compound of formula (V), which has an alkoxy or thioalkoxy (i.e., $-S-$ alkyl) group substitution on at least one tail:

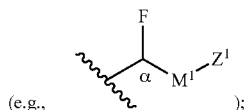


Formula (V)

or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

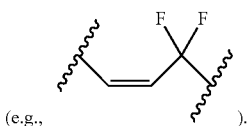
R', R¹, R², R, R³, R⁴, R¹⁰, Q, R⁵, M¹, M², a, and b are defined as in formula (I);

X and Y are each, independently, alkylene (e.g., C₆-C₈ alkylene) or alkenylene, wherein the alkylene or alkenylene group is optionally substituted with one or two fluorine atoms at the alpha position to the M¹ or M² group



(e.g., $-(CH_2)_n-$);

Z¹ and Z² are each, independently, C₈-C₁₄ alkyl or C₈-C₁₄ alkenyl, wherein (i) the C₈-C₁₄ alkyl or C₈-C₁₄ alkenyl of at least one of Z¹ and Z² is substituted by one or more alkoxy (e.g., a C₁-C₄ alkoxy such as $-OCH_3$) or thioalkoxy (e.g., a C₁-C₄ thioalkoxy such as $-SCH_3$) groups, and (ii) the alkenyl group may optionally be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of Z¹ or Z²



(e.g., $-(CH_2)_n-$).

In one embodiment, the alkoxy substitution on Z¹ and/or Z² is at the beta position from the M¹ and/or M² group.

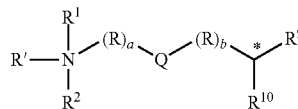
In another embodiment, X and Y are each, independently, $-(CH_2)_n-$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(CH_2)_6-$. In another embodiment, X and Y are $-(CH_2)_7-$. In yet another embodiment, X and Y are $-(CH_2)_9-$. In yet another embodiment, X and Y are $-(CH_2)_8-$.

The R'R¹R²N-(R)_a-Q-(R)_b group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, R'R¹R²N-(R)_a-Q-(R)_b is (CH₃)₂N-(CH₂)₃-C(O)O-, (CH₃)₂N-(CH₂)₂-NH-C(O)O-, (CH₃)₂N-(CH₂)₂-OC(O)-NH-, or (CH₃)₂N-(CH₂)₃-C(CH₃)=N-O-.

In one embodiment, the cationic lipid is a compound of formula (VIA), which has one or more fluoro substituents on at least one tail at a position that is either alpha to a double bond or alpha to a biodegradable group:

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Formula (VIA)



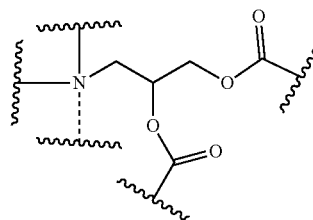
or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R¹, R², R, a, and b are as defined with respect to formula (I);

Q is absent or is $-O-$, $-NH-$, $-S-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(O)N(R^4)-$, $-N(R^5)C(O)-$, $-S-S-$, $-OC(O)O-$, $-O-N=C(R^5)-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-C(O)S-$, $-C(S)O-$ or $-C(R^5)=N-O-C(O)-$;

R' is absent, hydrogen, or alkyl (e.g., C₁-C₄ alkyl); and each of R⁹ and R¹⁰ are independently C₁₂-C₂₄ alkyl (e.g., C₁₂-C₂₀ alkyl), C₁₂-C₂₄ alkenyl (e.g., C₁₂-C₂₀ alkenyl), or C₁₂-C₂₄ alkoxy (e.g., C₁₂-C₂₀ alkoxy) (a) having one or more biodegradable groups and (b) optionally substituted with one or more fluorine atoms at a position which is (i) alpha to a biodegradable group and between the biodegradable group and the tertiary carbon atom marked with an asterisk (*), or (ii) alpha to a carbon-carbon double bond and between the double bond and the terminus of the R⁹ or R¹⁰ group; each biodegradable group independently interrupts the C₁₂-C₂₄ alkyl, alkenyl, or alkoxy group or is substituted at the terminus of the C₁₂-C₂₄ alkyl, alkenyl, or alkoxy group, wherein

- (i) at least one of R⁹ and R¹⁰ contains a fluoro group;
- (ii) the compound does not contain the following moiety:



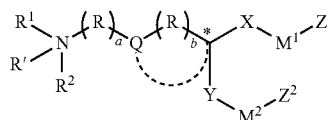
wherein ---- is an optional bond; and

(iii) the terminus of R⁹ and R¹⁰ is separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 8 or more atoms (e.g., 12 or 14 or more atoms).

In one preferred embodiment, the terminus of R⁹ and R¹⁰ is separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 18-22 carbon atoms (e.g., 18-20 carbon atoms).

In another embodiment, the terminus of the R⁹ and/or R¹⁰ has the formula $-C(O)O-CF_3$.

In another embodiment, the cationic lipid is a compound of formula (VIB), which has one or more fluoro substituents on at least one tail at a position that is either alpha to a double bond or alpha to a biodegradable group:



Formula (VIB)

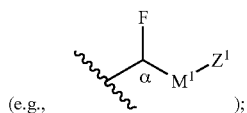
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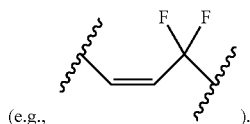
or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R¹, R¹, R², R, R³, R⁴, R¹⁰, Q, R⁵, M¹, M², a, and b are defined as in formula (I);

X and Y are each, independently, alkylene (e.g., C₆-C₈ alkylene) or alkenylene, wherein the alkylene or alkenylene group is optionally substituted with one or two fluorine atoms at the alpha position to the M¹ or M² group and



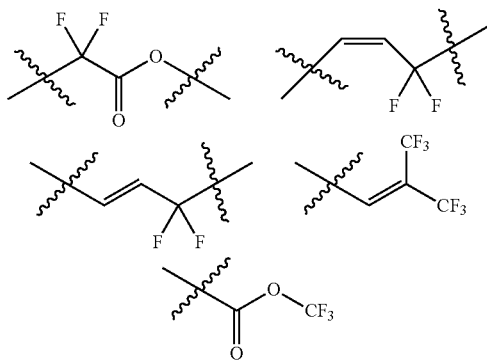
Z¹ and Z² are each, independently, C₈-C₁₄ alkyl or C₈-C₁₄ alkenyl, wherein said C₈-C₁₄ alkenyl is optionally substituted by one or more fluorine atoms at a position that is alpha to a double bond



wherein at least one of X, Y, Z¹, and Z² contains a fluorine atom.

In one embodiment, at least one of Z¹ and Z² is substituted by two fluoro groups at a position that is either alpha to a double bond or alpha to a biodegradable group. In one embodiment, at least one of Z¹ and Z² has a terminal —CF₃ group at a position that is alpha to a biodegradable group (i.e., at least one of Z¹ and Z² terminates with an —C(O)OCF₃ group).

For example, at least one of Z¹ and Z² may include one or more of the following moieties:



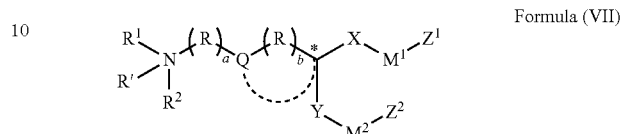
In one embodiment, X and Y are each, independently —(CH₂)_n wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are —(CH₂)₇—. In another exemplary embodiment, X and Y are —(CH₂)₉—. In yet another embodiment, X and Y are —(CH₂)₈—.

The R¹R¹R²N—(R)_a-Q-(R)_b— group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, R¹R¹R²N—(R)_a-Q-(R)_b— is (CH₃)₂N—(CH₂)₃—C

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(O)O—, (CH₃)₂N—(CH₂)₂—NH—C(O)O—, (CH₃)₂N—(CH₂)₂—OC(O)—NH—, or (CH₃)₂N—(CH₂)₃—C(CH₃)=N—O—.

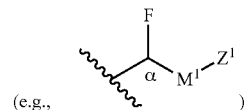
In one embodiment, the cationic lipid is a compound of formula (VII), which has an acetal group as a biodegradable group in at least one tail:



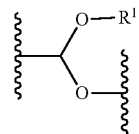
or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

R¹, R¹, R², R, R³, R⁴, R¹⁰, Q, R⁵, a, and b are defined as in formula (I);

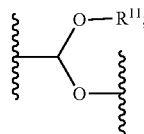
X and Y are each, independently, alkylene (e.g., C₆-C₈ alkylene) or alkenylene, wherein the alkylene or alkenylene group is optionally substituted with one or two fluorine atoms at the alpha position to the M¹ or M² group



M¹ and M² are each, independently, a biodegradable group (e.g., —OC(O)—, —C(O)O—, —SC(O)—, —C(O)S—, —OC(S)—, —C(S)O—, —S—S—, —C(R⁵)=N—, —N=C(R⁵)—, —C(R⁵)=N—O—, —O—N=C(R⁵)—, —C(O)(NR⁵)—, —N(R⁵)C(O)—, —C(S)(NR⁵)—, —N(R⁵)C(O)—, —N(R⁵)C(O)N(R⁵)—, —OC(O)O—, —OSi(R⁵)₂O—, —C(O)(CR³R⁴)C(O)O—, —OC(O)(CR³R⁴)C(O)—, or



(wherein R¹¹ is a C₄-C₁₀ alkyl or C₄-C₁₀ alkenyl); with the proviso that at least one of M¹ and M² is

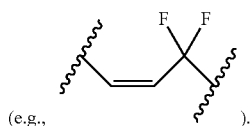


and

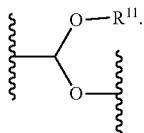
Z¹ and Z² are each, independently, C₄-C₁₄ alkyl or C₄-C₁₄ alkenyl, wherein the alkenyl group may optionally be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of Z¹ or Z²

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In one embodiment, each of M^1 and M^2 is

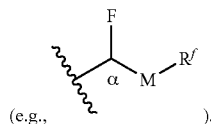


In another embodiment, X and Y are each, independently $-(CH_2)_n-$ wherein n is 4 to 20, e.g., 4 to 18, 4 to 16, or 4 to 12. In one embodiment, n is 4, 5, 6, 7, 8, 9, or 10. In one exemplary embodiment, X and Y are $-(CH_2)_6-$. In another embodiment, X and Y are $-(CH_2)_7-$. In yet another embodiment, X and Y are $-(CH_2)_9-$. In yet another embodiment, X and Y are $-(CH_2)_8-$.

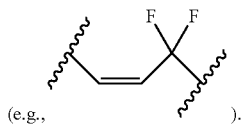
The $R^1R^2N-(R)_a-Q-(R)_b-$ group can be any of the head groups described herein, including those shown in Table 1 below, and salts thereof. In one preferred embodiment, $R^1R^2N-(R)_a-Q-(R)_b-$ is $(CH_3)_2N-(CH_2)_3-C(O)O-$, $(CH_3)_2N-(CH_2)_2-NH-C(O)O-$, $(CH_3)_2N-(CH_2)_2-OC(O)-NH-$, or $(CH_3)_2N-(CH_2)_3-C(CH_3)=N-O-$.

In another embodiment, the present invention relates to a cationic lipid or a salt thereof having:

- (i) a central carbon atom,
- (ii) a nitrogen containing head group directly bound to the central carbon atom, and
- (iii) two hydrophobic tails directly bound to the central carbon atom, wherein each hydrophobic tail is of the formula $-R^e-M-R^f$ where R^e is a C_4-C_{14} alkyl or alkenyl, M is a biodegradable group, and R^f is a branched alkyl or alkenyl (e.g., a $C_{10}-C_{20}$ alkyl or $C_{10}-C_{20}$ alkenyl), such that (i) the chain length of $-R^e-M-R^f$ is at most 20 atoms (i.e. the total length of the tail from the first carbon atom after the central carbon atom to a terminus of the tail is at most 20), and (ii) the group $-R^e-M-R^f$ has at least 20 carbon atoms (e.g., at least 21 atoms). Optionally, the alkyl or alkenyl group in R^e may be substituted with one or two fluorine atoms at the alpha position to the M^1 or M^2 group



Also, optionally, the alkenyl group in R^f may be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of R^f



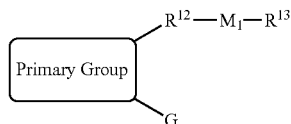
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In one embodiment, the cationic lipid of the present invention (such as of formulas I-VII) has asymmetrical hydrophobic groups (i.e., the two hydrophobic groups have different chemical formulas). For example, the cationic lipid can have the formula:

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Formula (VIII)

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or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), wherein

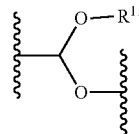
G is branched or unbranched C_3-C_{15} alkyl, alkenyl or alkynyl (e.g., a $n-C_8$ alkyl $n-C_9$ alkyl, or $n-C_{10}$ alkyl);

R^{12} is a branched or unbranched alkylene or alkenylene (e.g., C_6-C_{20} alkylene or C_6-C_{20} alkenylene such as $C_{12}-C_{20}$ alkylene or $C_{12}-C_{20}$ alkenylene);

M_1 is a biodegradable group (e.g., $-OC(O)-$, $-C(O)O-$, $-SC(O)-$, $-C(O)S-$, $-OC(S)-$, $-C(S)O-$, $-S-S-$, $-C(R^5)=N-$, $-N=C(R^5)-$, $-C(R^5)=N-O-$, $-O-N=C(R^5)-$, $-C(O)(NR^5)-$, $-N(R^5)C(O)-$, $-C(S)(NR^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)N(R^5)-$, $-OC(O)O-$, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, $-OC(O)(CR^3R^4)C(O)-$, or

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(wherein R^{11} is a C_2-C_8 alkyl or alkenyl);

R^3 and R^4 are defined as in formula (I);

each occurrence of R^5 is, independently, H or alkyl (e.g., C_1-C_4 alkyl);

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R^{13} is branched or unbranched C_3-C_{15} alkyl, alkenyl or alkynyl;

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Primary Group

comprises a protonatable group having a pK_a of from about 4 to about 13, more preferably from about 5 to about 8 (e.g. from about 5 to about 7, or from about 5 to about 6.5, or from about 5.5 to about 6.5, or from about 6 to about 6.5).

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In one embodiment, the primary group includes (i) a head group, and (ii) a central moiety (e.g., a central carbon atom) to which both the hydrophobic tails are directly bonded. Representative central moieties include, but are not limited to, a central carbon atom, a central nitrogen atom, a central carbocyclic group, a central aryl group, a central heterocyclic group (e.g., central tetrahydrofuranyl group or central pyrrolidinyl group) and a central heteroaryl group.

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Representative

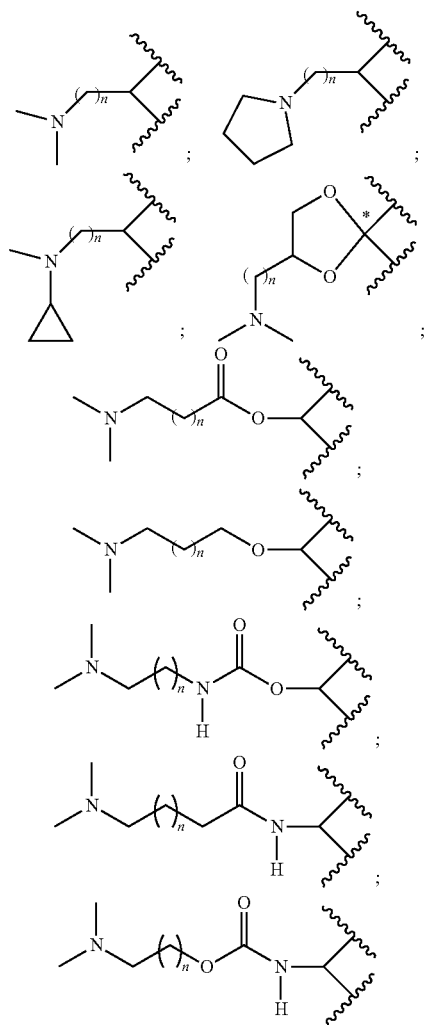
Primary Group's

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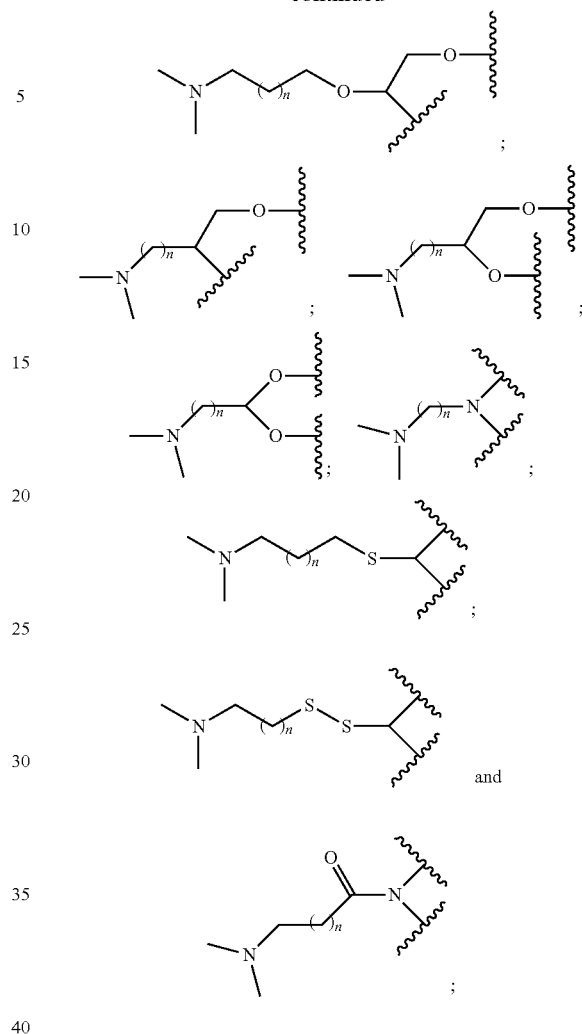
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include, but are not limited to,



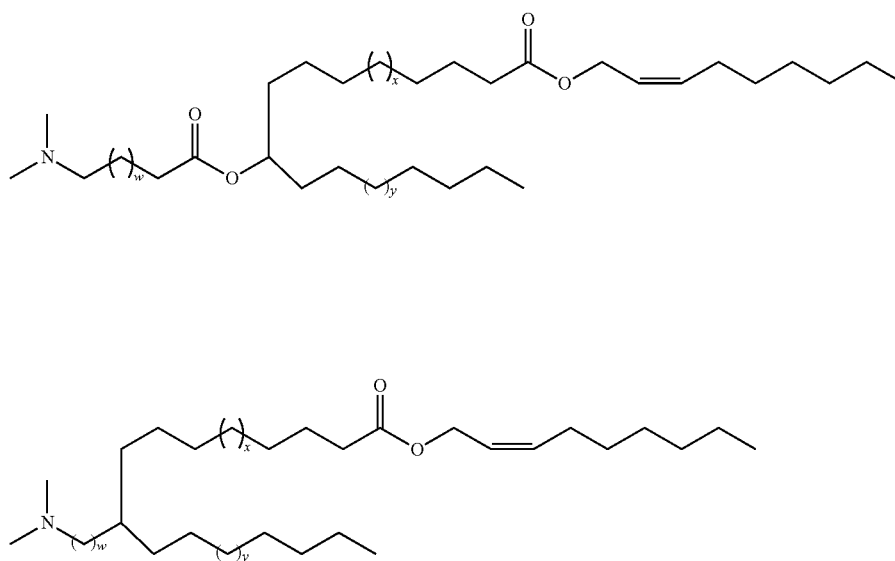
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-continued



where n is 0-6.

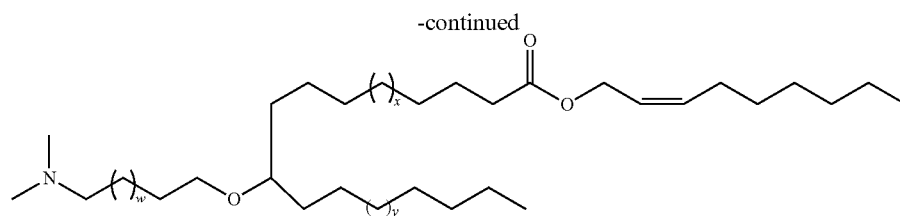
Representative asymmetrical cationic lipids include:



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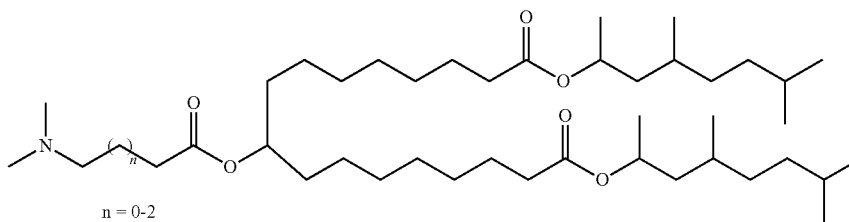
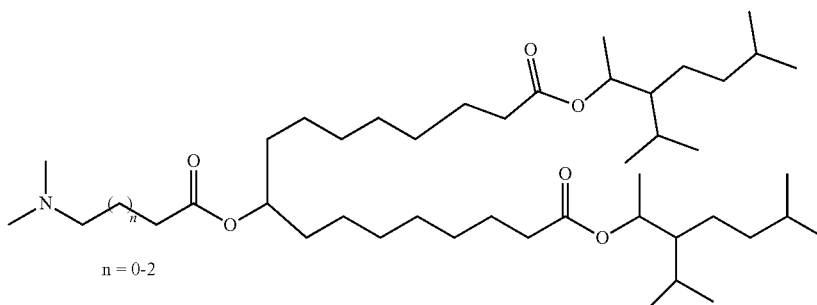
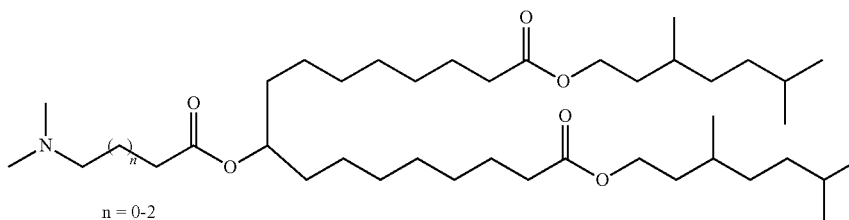
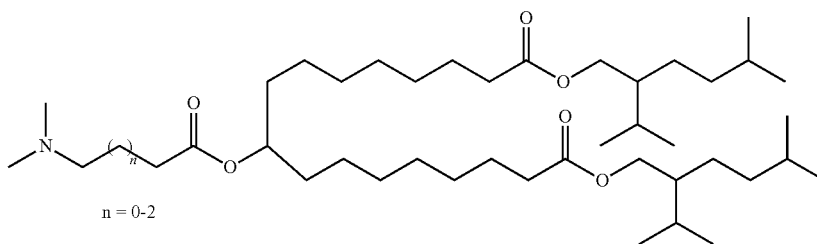
wherein w is 0, 1, 2, or 3; and x and y are each independently 1, 2, 3, 4, 5, 6, or 7.

In a preferred embodiment of the aforementioned biodegradable cationic lipids, the biodegradable cationic lipid has a log P value of at least 10.1 (as calculated by the software available at <http://www.molinspiration.com/services/logp.html> from Molinspiration Cheminformatics of Slovensky Grob, Slovak Republic). More preferably, the log P value is at least 10.2 or 10.3.

In another preferred embodiment of the aforementioned biodegradable cationic lipids, the biodegradable cationic

lipid in the lipid nanoparticle has a HPLC retention time (relative to the retention time of cholesterol in the lipid nanoparticle), hereafter referred to as $t_{lipid}-t_{choi}$, of at least 1.4. (The HPLC parameters are provided in the examples below. Unless otherwise specified, the formulation of the lipid nanoparticle used is that described in Example 31). More preferably, the $t_{lipid}-t_{choi}$ value is at least 1.75, 2.0, or 2.25.

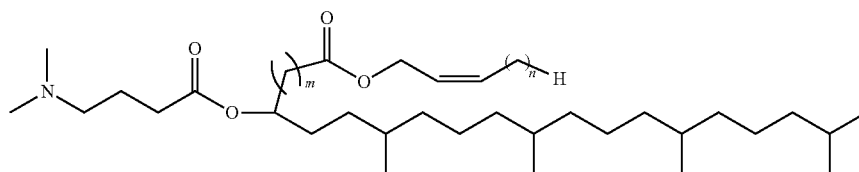
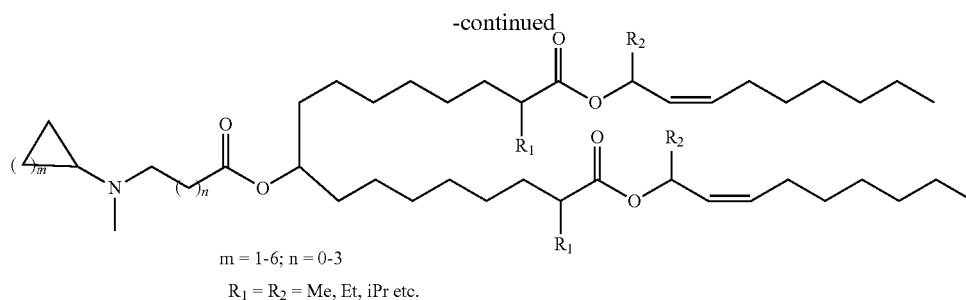
In another embodiment, the biodegradable cationic lipid of the present invention is not one selected from:



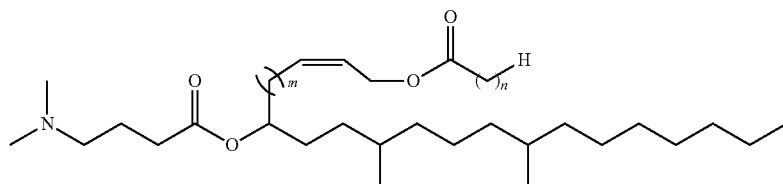
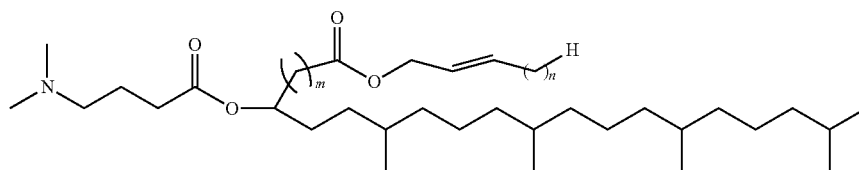
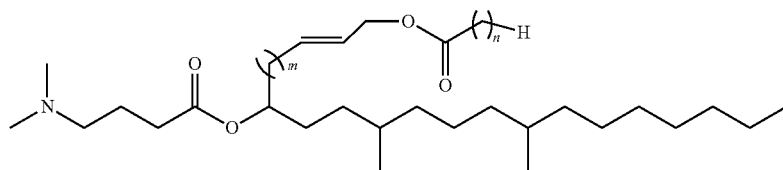
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where m and n are integers, and $m+n=13$ where m and n are integers, and $m+n=13$ where m and n are integers, and $m+n=13$ 

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where m and n are integers, and $m+n=13$

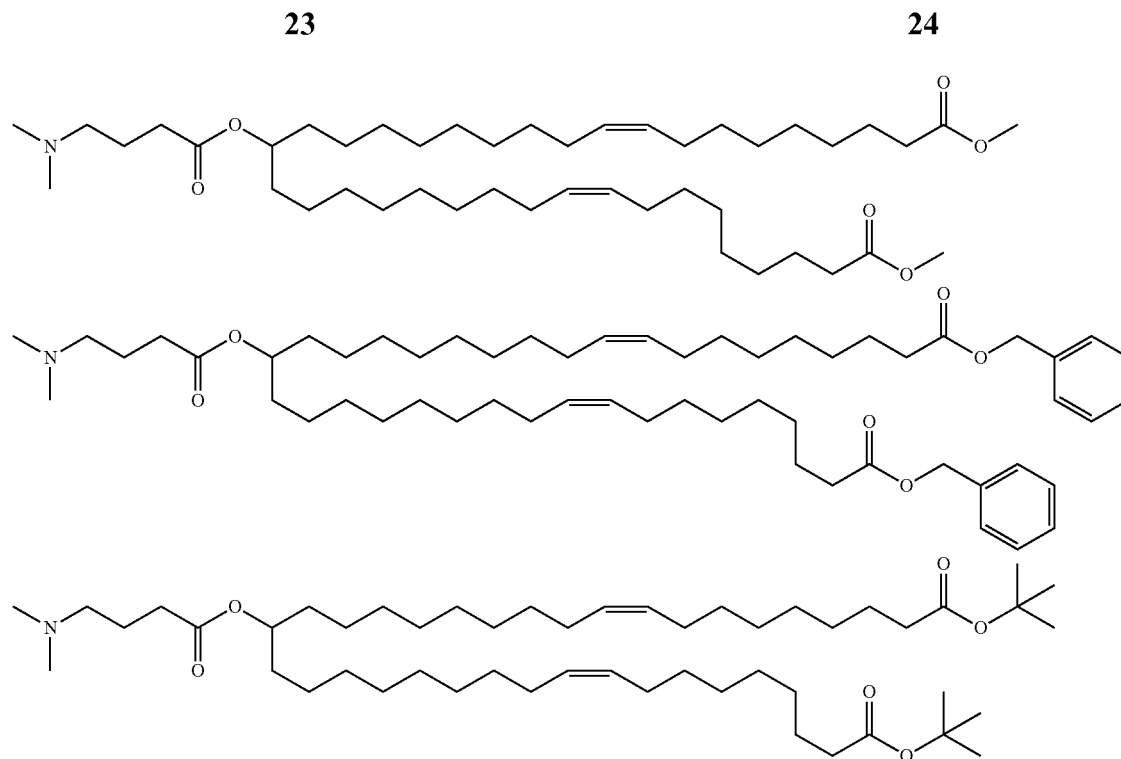
In yet another embodiment, the biodegradable cationic lipid is not one selected from those disclosed in International Publication No. WO 2011/153493 and U.S. Patent Publication No. 2012/0027803, both of which are hereby incorporated by reference.

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Yet another embodiment is a biodegradable cationic lipid having (i) a log P value of at least 10.1 and/or a $t_{lipid} - t_{chol}$ of at least 1.4, and (2) one or more biodegradable groups (such as an ester group) located in the mid- or distal section of a lipidic moiety (e.g., a hydrophobic chain) of the cationic lipid, with the proviso that the compound is not selected from

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In another embodiment, the biodegradable cationic lipid is not one selected from those disclosed in International Publication No. WO 2011/153493 and U.S. Patent Publication No. 2012/0027803, both of which are hereby incorporated by reference. The incorporation of the biodegradable group (s) into the cationic lipid results in faster metabolism and removal of the cationic lipid from the body following delivery of the active pharmaceutical ingredient to a target area. In a preferred embodiment, the cationic lipid includes a branched alkyl or branched alkenyl group in its biodegradable group(s). In another preferred embodiment, the cationic lipid has a log P of at least 10.2 or 10.3. In yet another preferred embodiment, the cationic lipid has a $t_{lipid}-t_{chole}$ of at least 1.75, 2.0, or 2.25. The cationic lipid preferably has a pKa of from about 4 to about 7 (such as 6.0 to 6.5).

In one embodiment, the cationic lipid having a log P value of at least 10.1 and/or a $t_{lipid}-t_{chole}$ of at least 1.4 comprises (a) a head group (preferably a nitrogen containing head group, such as the head groups described herein), (b) at least two hydrophobic tails, each of the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain), and (c) a linker group (for instance, a single central carbon atom) which is bound to the head group and the hydrophobic tails. The cationic lipid preferably has one, two, three, four or more of the properties listed below:

(i) a pKa of from about 4 to about 7 (such as 6.0 to 6.5);

(ii) in at least one hydrophobic tail (and preferably all hydrophobic tails), the biodegradable group is separated from the terminus of the hydrophobic tail by from about 6 to about 12 carbon atoms (for instance, 6 to 8 carbon atoms or 8 to 12 carbon atoms),

(iii) for at least one hydrophobic tail (and preferably all hydrophobic tails), the chain length from the linker group to the terminus of the hydrophobic tail is at most 21 (e.g., at most 20, or from about 17 to about 21, from about 18 to

about 20, or from about 16 to about 18) (The atom(s) in the linker group are not counted when calculating the chain length.);

(iv) for at least one hydrophobic tail (and preferably all hydrophobic tails), the total number of carbon atoms in the hydrophobic tail is from about 17 to about 26 (such as from about 19 to about 26, or from about 21 to about 26);

(v) for at least one hydrophobic tail (and preferably all hydrophobic tails), the number of carbon atoms between the linker group and the biodegradable group ranges from about 5 to about 10 (for example, 6 to 10, or 7 to 9);

(vi) for at least one hydrophobic tail (and preferably all hydrophobic tails), the total number of carbon atoms between the linker group and the terminus of the hydrophobic tail is from about 15 to about 20 (such as from 16 to 20, 16 to 18, or 18 to 20);

(vii) for at least one hydrophobic tail (and preferably all hydrophobic tails), the total number of carbon atoms between the biodegradable group and the terminus of the hydrophobic tail is from about 12 to about 18 (such as from 13 to 25);

(viii) for at least one hydrophobic tail (and preferably all hydrophobic tails), the terminal hydrophobic chain in the hydrophobic tail is a branched alkyl or alkenyl group, for example, where the branching occurs at the α , β , γ , or δ position on the hydrophobic chain relative to the biodegradable group;

(ix) when formulated as a lipid nanoparticle (such as in Example 35), the cationic lipid has an in vivo half life ($t_{1/2}$) in the liver of less than about 3 hours, such as less than about 2.5 hours, less than about 2 hours, less than about 1.5 hours, less than about 1 hour, less than about 0.5 hour or less than about 0.25 hours;

(x) when formulated as a lipid nanoparticle (such as in Example 35), the cationic lipid is eliminated from the liver in mice with a greater than 10-fold reduction in lipid levels relative to C_{max} within the first 24 hours post-dose;

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(xi) when formulated as a lipid nanoparticle (such as in Example 35), the cationic lipid is eliminated from the spleen in mice with an equal or greater than 10-fold reduction in lipid levels relative to C_{max} within the first 168 hours post-dose; and

(xii) when formulated as a lipid nanoparticle (such as in Example 35), the cationic lipid is eliminated from plasma with a terminal plasma half-life ($t_{1/2\beta}$) in rodents and non-human primates of 48 hours or shorter.

The present invention embodies compounds having any combination of some or all of the aforementioned properties. These properties provide a cationic lipid which remains intact until delivery of an active agent, such as a nucleic acid, after which cleavage of the hydrophobic tail occurs in vivo. For instance, the compounds can have all of properties (i) to (viii) (in addition to the log P or $t_{lipid}-t_{chol}$ value). In another embodiment, the compounds have properties (i), (ii), (iii), and (viii). In yet another embodiment, the compounds have properties (i), (ii), (iii), (v), (vi), and (viii).

Another embodiment is a method of preparing a cationic lipid comprising:

(a) designing a cationic lipid having a log P value of at least 10.1 and/or a $t_{lipid}-t_{chole}$ of at least 1.4, and optionally also having one, two, three, four, or more properties from the list above (i.e., properties (i)-(xii)); and

(b) synthesizing the cationic lipid of step (a). The cationic lipid in step (a) may comprises (a) a head group (preferably a nitrogen containing head group, such as the head groups described herein), (b) at least two hydrophobic tails, each of the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain), and (c) a linker group (for instance, a single central carbon atom) which is bound to the head group and the hydrophobic tails. Step (a) may comprise:

(a)(i) preparing one or more cationic lipids having a log P value of at least 10.1 and/or a $t_{lipid} - t_{cho}b$ of at least 1.4, and optionally also having one, two, three, four, or more properties from the list above (i.e., properties (i)-(xii));

(a)(ii) screening the cationic lipids to determine their efficacy and/or toxicity in lipid nanoparticles; and

(a)(iii) selecting a cationic lipid for synthesis.

Yet another embodiment is a method of designing a cationic lipid comprising:

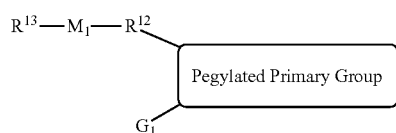
(a) selecting a cationic lipid having a log P value of at least 10.1 and/or a $t_{lipid}-t_{chole}$ of at least 1.4, and optionally also having one, two, three, four, or more properties from the list above (i.e., properties (i)-(xii)); and

(b) optionally,

(i) preparing one or more cationic lipids having a log P value of at least 10.1 and/or a $t_{lipid}-t_{chole}$ of at least 1.4, and optionally also having one, two, three, four, or more properties from the list above (i.e., properties (i)-(xii));

- (ii) screening the cationic lipids to determine their efficacy and/or toxicity in lipid nanoparticles; and
- (iii) optionally, selecting a cationic lipid for further development or use.

In one embodiment, the PEG lipid has the formula:



Formula (IX)

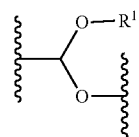
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wherein

G₁ is branched or unbranched C₃-C₁₅ alkyl, alkenyl or alkynyl (e.g., a n-C₈ alkyl n-C₉ alkyl, or n-C₁₀ alkyl); or G₁ is —R¹²-M₁-R¹³;

R¹² is a branched or unbranched alkylene or alkenylene (e.g., C₆-C₂₀ alkylene or C₆-C₂₀ alkenylene such as C₁₂-C₂₀ alkylene or C₁₂-C₂₀ alkenylene);

M₁ is a biodegradable group (e.g., —OC(O)—, —C(O)O—, —SC(O)—, —C(O)S—, —OC(S)—, —C(S)O—, —S—S—, —C(R⁵)=N—, —N—C(R⁵)—, —C(R⁵)=N—O—, —O—N=C(R⁵)—, —C(O)(NR⁵)—, —N(R⁵)C(O)—, —C(S)(NR⁵)—, —N(R⁵)C(O)—, —N(R⁵)C(O)N(R⁵)—, —OC(O)O—, —OSi(R⁵)₂O—, —C(O)(CR³R⁴)C(O)O—, —OC(O)(CR³R⁴)C(O)—, or

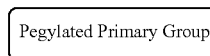


(wherein R¹¹ is a C₂-C₈ alkyl or alkenyl));

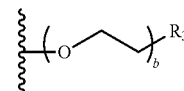
R^3 and R^4 are defined as in formula (I):

each occurrence of R⁵ is, independently, H or alkyl (e.g., 1-C₄ alkyl);

R¹³ is branched or unbranched C₃-C₁₅ alkyl, alkenyl or alkynyl;



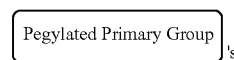
comprises a PEG moiety, such as



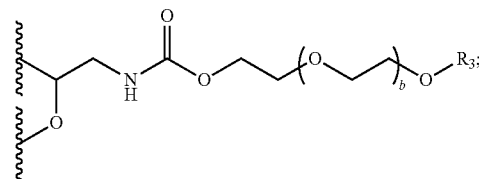
moiety wherein b is an integer from 10 to 1,000 (e.g., 5-100, 10-60, 15-50, or 20-45); R^3 is —H, —R^c, or —OR^c; and R^c is —H, alkyl, acyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl.

In one embodiment, the pegylated primary group includes (i) a head group having a PEG moiety, and (ii) a central moiety (e.g., a central carbon atom) to which both the hydrophobic tails are directly bonded. Representative central moieties include, but are not limited to, a central carbon atom, a central nitrogen atom, a central carbocyclic group, a central aryl group, a central heterocyclic group (e.g., central tetrahydrofuranyl group or central pyrrolidinyl group) and a central heteroaryl group.

Representative

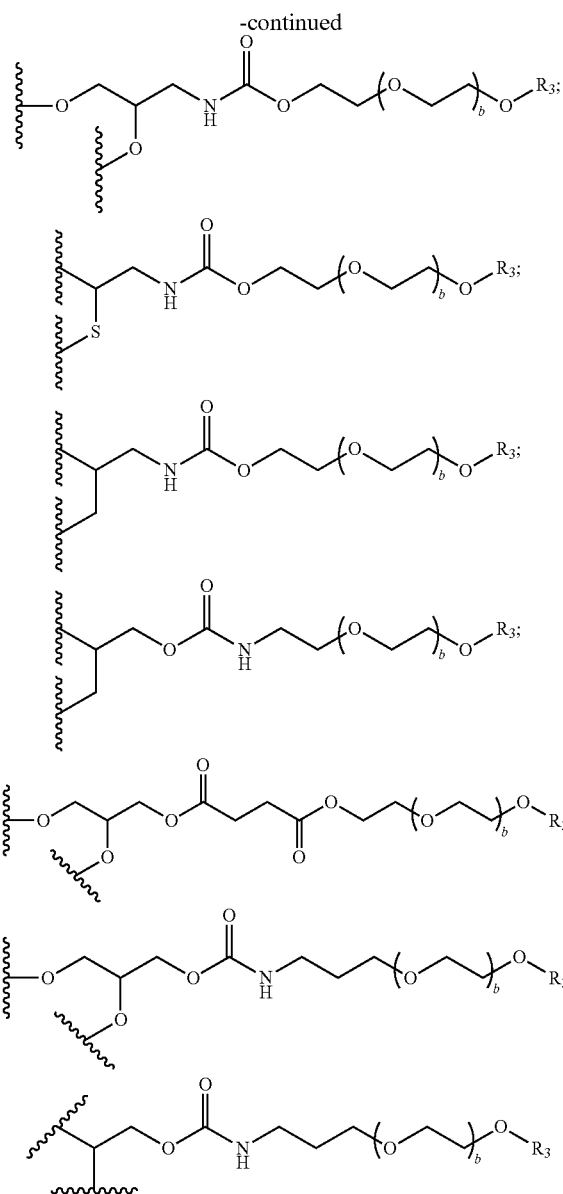


include, but are not limited to,



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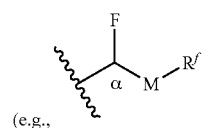
where b is 10-100 (e.g., 20-50 or 40-50)

Another embodiment of the present invention is a PEG lipid (or a salt thereof) having:

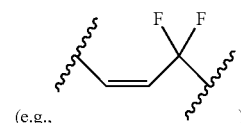
(i) a pegylated primary group including a head group which includes a PEG moiety (e.g., having from 10 to 1000 repeating units such as ethoxy units), and

(iii) one or more hydrophobic tails (preferably, two hydrophobic tails) directly bound to the pegylated primary group, wherein at least one hydrophobic tail is of the formula $\text{—R}^e\text{—M—R}^f$ where R^e is a $\text{C}_4\text{—C}_{14}$ alkyl or alkenyl, M is a biodegradable group, and R^f is a branched alkyl or alkenyl (e.g., a $\text{C}_{10}\text{—C}_{20}$ alkyl or $\text{C}_{10}\text{—C}_{20}$ alkenyl), such that (i) the chain length of $\text{—R}^e\text{—M—R}^f$ is at most 20 atoms (i.e. the total length of the tail from the first carbon atom after the central carbon atom to a terminus of the tail is at most 20), and (ii) the group $\text{—R}^e\text{—M—R}^f$ has at least 20 carbon atoms (e.g., at least 21 atoms). Optionally, the alkyl or alkenyl group in R^e may be substituted with one or two fluorine atoms at the alpha position to the M^1 or M^2 group

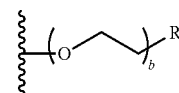
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Also, optionally, the alkenyl group in R^f may be substituted with one or two fluorine atoms at the alpha position to a double bond which is between the double bond and the terminus of R^f



In one embodiment, the pegylated primary group includes (i) a head group having a PEG moiety, and (ii) a central moiety (e.g., a central carbon atom) to which the hydrophobic tails are directly bound. The PEG moiety may have 5-100, 10-60, 15-50, or 20-45 repeating units. For example, the PEG moiety may have the formula



moiety wherein b is an integer from 10 to 1,000 (e.g., 5-100, 10-60, 15-50, or 20-45); R^3 is —H , —R^c , or —OR^c ; and R^c is —H , alkyl (e.g., $\text{C}_1\text{—C}_4$ alkyl), acyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl.

Yet another embodiment is a lipid particle that includes a cationic lipid and/or PEG lipid of the present invention. In one embodiment, the lipid particle includes a cationic lipid of the present invention (e.g., of one of formulas (I)-(VIII)). In another embodiment, the lipid particle includes a PEG lipid of the present invention (e.g., of formula (IX)). In yet another embodiment, the lipid particle includes a cationic lipid of the present invention and a PEG lipid of the present invention.

In a preferred embodiment, the lipid particle includes a neutral lipid, a lipid capable of reducing aggregation, a cationic lipid, and optionally, a sterol (e.g., cholesterol). Suitable neutral lipids include, but are not limited to, distearoylphosphatidylcholine (DSPC), dipalmitoylphosphatidylcholine (DPPC), POPC, DOPE, and SM. Suitable lipids capable of reducing aggregation include, but are not limited to, a PEG lipid, such as PEG-DMA, PEG-DMG, and those of the present invention (e.g., of formula (IX)) or a combination thereof.

The lipid particle may further include an active agent (e.g., a therapeutic agent). The active agent can be a nucleic acid such as a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, or a ribozyme. In a preferred embodiment, the nucleic acid is a siRNA. In another preferred embodiment, the nucleic acid is a miRNA.

In another embodiment, the lipid particle includes a cationic lipid of the present invention, a neutral lipid and a sterol. The lipid particle may further include an active agent, such as a nucleic acid (e.g., an siRNA or miRNA).

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In yet another embodiment, the lipid particle includes a PEG lipid of the present invention, a cationic lipid, a neutral lipid, and a sterol. The lipid particle may further include an active agent, such as a nucleic acid (e.g., an siRNA or miRNA).

The lipid particles described herein may be lipid nanoparticles.

Yet another embodiment of the invention is a pharmaceutical composition which includes a lipid particle of the present invention and a pharmaceutically acceptable carrier.

In one embodiment, the cationic lipid remains intact until delivery of the nucleic acid molecule after which cleavage of the hydrophobic tail occurs in vivo.

In another embodiment, the PEG lipid remains intact until delivery of the nucleic acid molecule after which cleavage of the hydrophobic tail occurs in vivo.

In another embodiment, the present invention relates to a method of delivering a nucleic acid molecule comprising administering a nucleic acid molecule comprising (i) the nucleic acid molecule and (ii) a cationic lipid and/or a PEG lipid of the present invention. In one embodiment, the cationic lipid and/or a PEG lipid remains intact until delivery of the nucleic acid molecule after which cleavage of the hydrophobic tail occurs in vivo.

Yet another aspect is a method of modulating the expression of a target gene in a cell by providing to the cell a lipid particle of the present invention. The active agent can be a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme. In a preferred embodiment, the nucleic acid is a siRNA or miRNA.

Yet another aspect is a method of treating a disease or disorder characterized by the overexpression of a polypeptide in a subject by providing to the subject a pharmaceutical composition of the present invention, wherein the active agent is a nucleic acid selected from an siRNA, a microRNA, and an antisense oligonucleotide, and wherein the siRNA, microRNA, or antisense oligonucleotide includes a polynucleotide that specifically binds to a polynucleotide that encodes the polypeptide, or a complement thereof. In a preferred embodiment, the nucleic acid is a siRNA or miRNA.

Yet another aspect is a method of treating a disease or disorder characterized by underexpression of a polypeptide in a subject by providing to the subject a pharmaceutical composition of the present invention, wherein the active agent is a plasmid that encodes the polypeptide or a functional variant or fragment thereof.

Yet another aspect is a method of inducing an immune response in a subject by providing to the subject a pharmaceutical composition wherein the active agent is an immunostimulatory oligonucleotide.

Yet another aspect is a transfection agent that includes the composition or lipid particles described above, where the composition or lipid particles include a nucleic acid. The agent, when contacted with cells, can efficiently deliver nucleic acids to the cells. Yet another aspect is a method of delivering a nucleic acid to the interior of a cell, by obtaining or forming a composition or lipid particles described above, and contacting the composition or lipid particles with a cell.

DETAILED DESCRIPTION

In one aspect, the present invention relates to a lipid particle that includes a neutral lipid, a lipid capable of reducing aggregation (e.g., a PEG lipid), a cationic lipid, and

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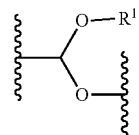
optionally a sterol. In certain embodiments, the lipid particle further includes an active agent (e.g., a therapeutic agent). Various exemplary embodiments of these lipids, lipid particles and compositions comprising the same, and their use to deliver therapeutic agents and modulate gene and protein expression are described in further detail below.

The Cationic Lipid

In one embodiment, the cationic lipid is a compound of any one of Formulas I-VIII. The following disclosure represents various embodiments of the compounds described above, including the compounds of Formulas I-VIII.

In one embodiment, M^1 and M^2 are each, independently:

$-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(\text{O})\text{S}-$, $-\text{OC}(\text{S})-$, $-\text{C}(\text{S})\text{O}-$, $-\text{S}-\text{S}-$, $-\text{C}(\text{R}^5)=\text{N}-$, $-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^5)=\text{N}-\text{O}-$, $-\text{O}-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{O})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{C}(\text{S})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{N}(\text{R}^5)-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{OSi}(\text{R}^5)_2\text{O}-$, $-\text{C}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})-$, or



(wherein R^{11} is a C_2 - C_8 alkyl or alkenyl).

In another embodiment, M^1 and M^2 are each, independently:

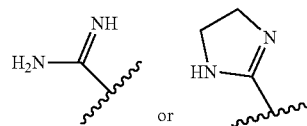
$-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{R}^5)=\text{N}-$, $-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^5)=\text{N}-\text{O}-$, $-\text{O}-\text{N}=\text{C}(\text{R}^5)-$, $-\text{O}-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{S}-$, $-\text{SC}(\text{O})-$, $-\text{C}(\text{S})\text{O}-$, $-\text{OC}(\text{S})-$, $-\text{OSi}(\text{R}^5)_2\text{O}-$, $-\text{C}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})\text{O}-$, or $-\text{OC}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})-$.

In yet another embodiment, M^1 and M^2 are each, independently:

$-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{R}^5)=\text{N}-$, $-\text{C}(\text{R}^5)=\text{N}-\text{O}-$, $-\text{O}-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{N}(\text{R}^5)-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{S})\text{O}-$, $-\text{OSi}(\text{R}^5)_2\text{O}-$, $-\text{C}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})\text{O}-$, or $-\text{OC}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})-$.

In another embodiment, M^1 and M^2 are each $-\text{C}(\text{O})\text{O}-$.

In one embodiment, R^1 and R^2 are each, individually, optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, or heterocycle. In one embodiment, R^1 is alkyl and R^2 is alkyl, cycloalkyl or cycloalkylalkyl. In one embodiment, R^1 and R^2 are each, individually, alkyl (e.g., C_1 - C_4 alkyl, such as methyl, ethyl, or isopropyl). In one embodiment, R^1 and R^2 are both methyl. In another embodiment, R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclic ring (e.g., N-methylpiperazinyl). In another embodiment, one of R^1 and R^2 is



(e.g., R^1 is one of the two aforementioned groups and R^2 is hydrogen).

In one embodiment, R' is hydrogen or alkyl. In another embodiment, R' is hydrogen or methyl. In one embodiment, R' is absent. In one embodiment, R' is absent or methyl.

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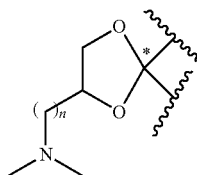
For cationic lipid compounds which contain an atom (e.g., a nitrogen atom) that carries a positive charge, the compound also contains a negatively charged counter ion. The counterion can be any anion, such as an organic or inorganic anion. Suitable examples of anions include, but are not limited to, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -keto-glutarate, α -glycerophosphate, halide (e.g., chloride), sulfate, nitrate, bicarbonate, and carbonate. In one embodiment, the counterion is a halide (e.g., Cl).

In one embodiment each R is, independently, $-(CR^3R^4)-$, wherein R^3 and R^4 are each, independently, H or alkyl (e.g., C_1 - C_4 alkyl). For example, in one embodiment each R is, independently, $-(CHR^4)-$, wherein each R^4 is, independently H or alkyl (e.g., C_1 - C_4 alkyl). In another embodiment, each R is, independently, $-CH_2-$, $-C(CH_3)_2-$ or $-CH(iPr)-$ (where iPr is isopropyl). In another embodiment, each R is $-CH_2-$.

In another embodiment R^5 is, in each case, hydrogen or methyl. For example, R^5 can be, in each case, hydrogen.

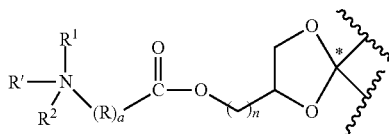
In one embodiment, Q is absent, $-C(O)O-$, $-OC(O)-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-S-S-$, $-OC(O)O-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, $-C(O)S-$, $-C(S)O-$ or $-C(R^5)=N-O-C(O)-$. In one embodiment, Q is $-C(O)O-$.

In one embodiment, the dashed line to Q is absent, b is 0 and $R'R^1R^2N-(R)_a-Q-$ and the tertiary carbon adjacent to it (C*) form the following group:



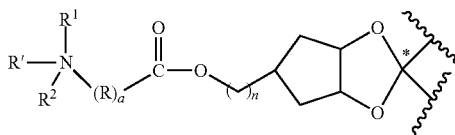
where n is 1 to 4 (e.g., n is 2).

In one embodiment, the dashed line to Q is absent, b is 0 and $R'R^1R^2N-(R)_a-Q-$ and the tertiary carbon adjacent to it form the following group:



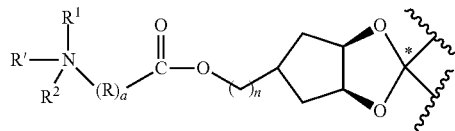
where n is 1 to 4 (e.g., n is 2), and R^1 , R^2 , R, a, and b are as defined with respect to formula (I). In one embodiment, a is 3.

In one embodiment, the dashed line to Q is absent, b is 0 and $R'R^1R^2N-(R)_a-Q-$ and the tertiary carbon adjacent to it form the following group:



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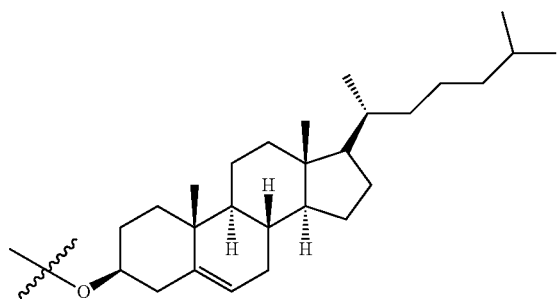
where n is 1 to 4 (e.g., n is 2), and R^1 , R^2 , R, a, and b are as defined with respect to formula (I). In one embodiment, a is 0. For example, the group can be:



In one embodiment, b is 0. In another embodiment, a is 2, 3, or 4 and b is 0. For example, in one embodiment, a is 3 and b is 0. In another embodiment, a is 3, b is 0, and Q is $-C(O)O-$.

In certain embodiments, the biodegradable group present in the cationic lipid is selected from an ester (e.g., $-C(O)O-$ or $-OC(O)-$), disulfide ($-S-S-$), oxime (e.g., $-C(H)=N-O-$ or $-O-N=C(H)-$), $-C(O)-O-$, $-OC(O)-$, $-C(R^5)=N-$, $-N=C(R^5)-$, $-C(R^5)=N-O-$, $-O-N=C(R^5)-$, $-O-C(O)O-$, $-C(O)N(R^5)-$, $-N(R^5)C(O)-$, $-C(S)(NR^5)-$, $(NR^5)C(S)-$, $-N(R^5)C(O)N(R^5)-$, $-C(O)S-$, $-SC(O)-$, $-C(S)O-$, $-OC(S)-$, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, or $-OC(O)(CR^3R^4)C(O)-$.

A suitable cholesterol moiety for the cationic lipids of the present invention (including compounds of formulas I-VI) has the formula:



Additional embodiments include a cationic lipid having a head group, one or more hydrophobic tails, and a central moiety between the head group and the one or more tails. The head group can include an amine; for example an amine having a desired pK_a . The pK_a can be influenced by the structure of the lipid, particularly the nature of head group; e.g., the presence, absence, and location of functional groups such as anionic functional groups, hydrogen bond donor functional groups, hydrogen bond acceptor groups, hydrophobic groups (e.g., aliphatic groups), hydrophilic groups (e.g., hydroxyl or methoxy), or aryl groups. The head group amine can be a cationic amine; a primary, secondary, or tertiary amine; the head group can include one amine group (monoamine), two amine groups (diamine), three amine groups (triamine), or a larger number of amine groups, as in an oligoamine or polyamine. The head group can include a functional group that is less strongly basic than an amine, such as, for example, an imidazole, a pyridine, or a guanidinium group. The head group can be zwitterionic. Other head groups are suitable as well.

Representative central moieties include, but are not limited to, a central carbon atom, a central nitrogen atom, a central carbocyclic group, a central aryl group, a central

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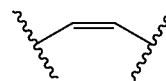
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hetrocyclic group (e.g., central tetrahydrofuranyl group or central pyrrolidinyl group) and a central heteroaryl group. Additionally, the central moiety can include, for example, a glyceride linker, an acyclic glyceride analog linker, or a cyclic linker (including a spiro linker, a bicyclic linker, and a polycyclic linker). The central moiety can include functional groups such as an ether, an ester, a phosphate, a phosphonate, a phosphorothioate, a sulfonate, a disulfide, an acetal, a ketal, an imine, a hydrazone, or an oxime. Other central moieties and functional groups are suitable as well.

In one embodiment, the cationic lipid is a racemic mixture. In another embodiment, the cationic lipid is enriched in one diastereomer, e.g. the cationic lipid has at least 95%, at least 90%, at least 80% or at least 70% diastereomeric excess. In yet another embodiment, the cationic lipid is enriched in one enantiomer, e.g. the lipid has at least 95%, at least 90%, at least 80% or at least 70% enantiomer excess. In yet another embodiment, the cationic lipid is chirally pure, e.g. is a single optical isomer. In yet another embodiment, the cationic lipid is enriched for one optical isomer.

Where a double bond is present (e.g., a carbon-carbon double bond or carbon-nitrogen double bond), there can be isomerism in the configuration about the double bond (i.e. cis/trans or E/Z isomerism). Where the configuration of a double bond is illustrated in a chemical structure, it is understood that the corresponding isomer can also be present. The amount of isomer present can vary, depending on the relative stabilities of the isomers and the energy required to convert between the isomers. Accordingly, some double bonds are, for practical purposes, present in only a single configuration, whereas others (e.g., where the relative sta-

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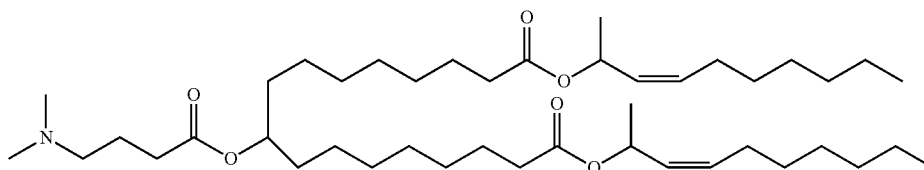
can be replaced by



The cationic lipid includes one or more biodegradable groups. The biodegradable group(s) include one or more bonds that may undergo bond breaking reactions in a biological environment, e.g., in an organism, organ, tissue, cell, or organelle. Functional groups that contain a biodegradable bond include, for example, esters, dithiols, and oximes. Biodegradation can be a factor that influences the clearance of the compound from the body when administered to a subject. Biodegradation can be measured in a cell based assay, where a formulation including a cationic lipid is exposed to cells, and samples are taken at various time points. The lipid fractions can be extracted from the cells and separated and analyzed by LC-MS. From the LC-MS data, rates of biodegradation (e.g., as $t_{1/2}$ values) can be measured.

For example, the compound

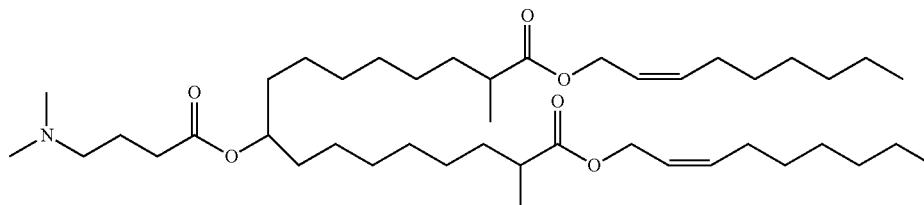
(Compound 1)



bilities are similar and the energy of conversion low) may be present as inseparable equilibrium mixture of configurations.

In some cases, a double-bonded unsaturation is replaced by a cyclic unsaturation. The cyclic unsaturation can be a cycloaliphatic unsaturation, e.g., a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl group.

includes an ester linkage in each aliphatic chain, which can undergo hydrolysis in a biological environment, for example, when exposed to, e.g., a lipase or an esterase. The structure of the compound, of course, influences the rate at which the compound undergoes biodegradation. Thus, a compound where the methyl substituent is on the other side of the biodegradable group such as



In some cases, the cyclic group can be a polycyclic group, e.g., a bicyclic group or tricyclic group. A bicyclic group can be bridged, fused, or have a spiro structure. In some cases, a double bond moiety can be replaced by a cyclopropyl moiety, e.g.,

would be expected to exhibit a different rate of biodegradation. Greater effects on that rate would be expected from changes in the structure of the compound at the site of hydrolysis. One modification that can influence the rate of hydrolysis, and thereby influence the rate of biodegradation

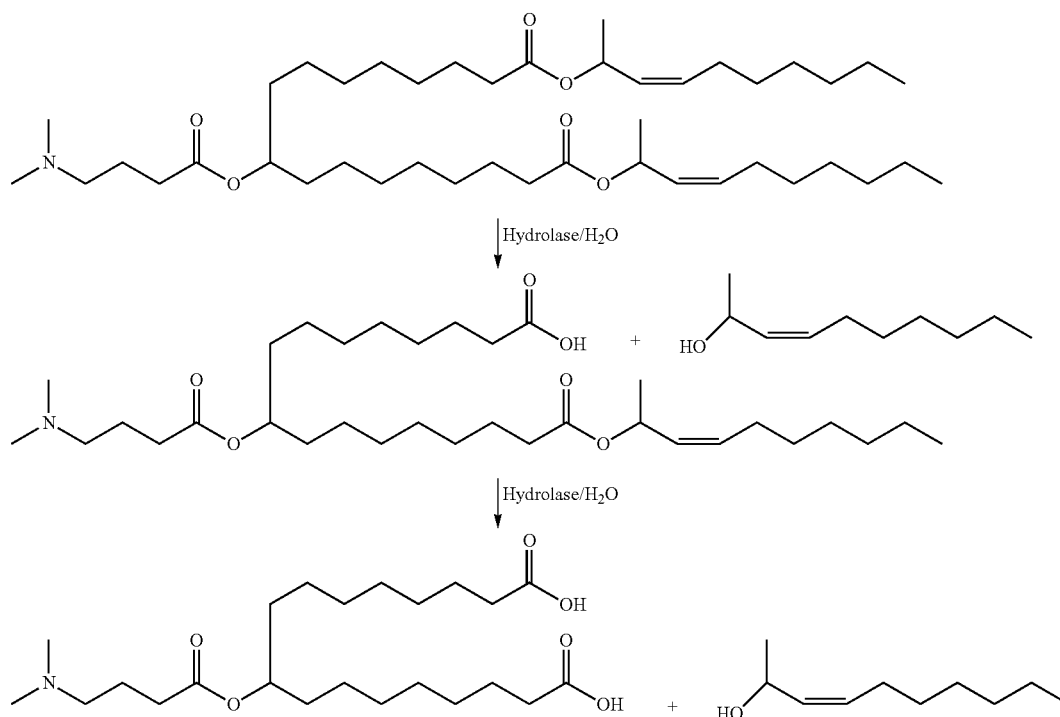
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and clearance from a subject's body, is to make the leaving group of the hydrolysis reaction have a secondary, rather than primary, alcohol.

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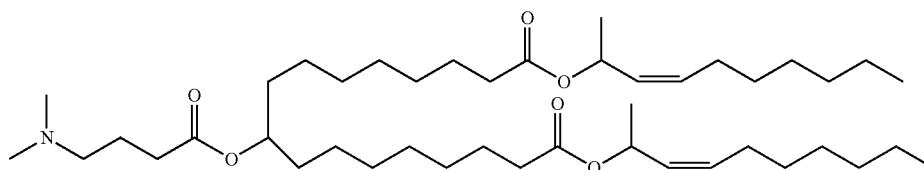
For example, without wishing to be bound by theory, Compound 1 shown above may be metabolized as shown in the scheme below:



35 In one embodiment, a cationic lipid of any of the embodiments described herein has an in vivo half life ($t_{1/2}$) (e.g., in the liver, spleen or plasma) of less than about 3 hours, such as less than about 2.5 hours, less than about 2 hours, less than about 1.5 hours, less than about 1 hour, less than about 0.5 hour or less than about 0.25 hours. The cationic lipid
40 preferably remains intact, or has a half-life sufficient to form a stable lipid nanoparticle which effectively delivers the desired active pharmaceutical ingredient (e.g., a nucleic acid) to its target but thereafter rapidly degrades to minimize any side effects to the subject. For instance, in mice, the cationic lipid preferably has a $t_{1/2}$ in the spleen of from about
45 1 to about 7 hours.

In another embodiment, a cationic lipid of any of the embodiments described herein containing a biodegradable group or groups has an in vivo half life ($t_{1/2}$) (e.g., in the liver, spleen or plasma) of less than about 10% (e.g., less
50 than about 7.5%, less than about 5%, less than about 2.5%) of that for the same cationic lipid without the biodegradable group or groups.

Some cationic lipids can be conveniently represented as a
55 hydrophobic group combined via a central moiety (such as a carbon atom) with a headgroup. By way of example, the compound:

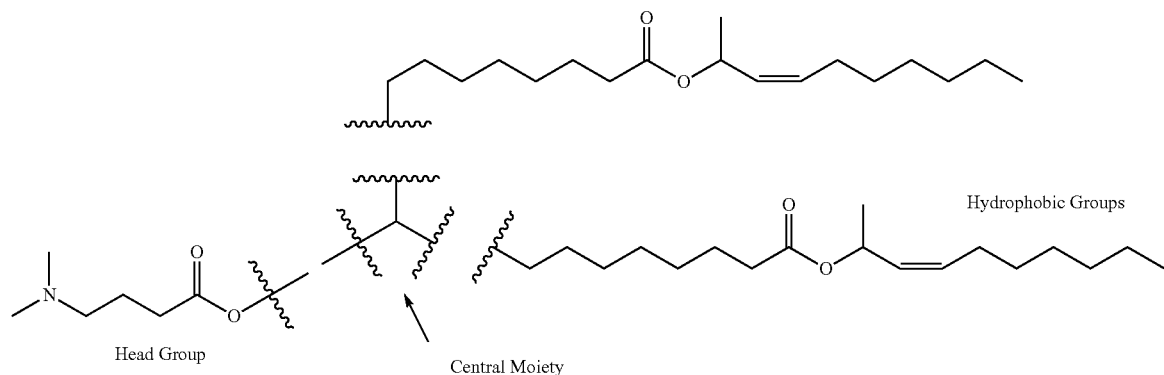


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can be thought of as a combination of a headgroup, a central moiety, and two hydrophobic groups as follows:



The present invention includes compounds composed of any combination of the head and hydrophobic groups listed below (in combination with a central moiety (such as a central carbon atom)).

Some suitable head groups include those depicted in Table 1A:

TABLE 1A

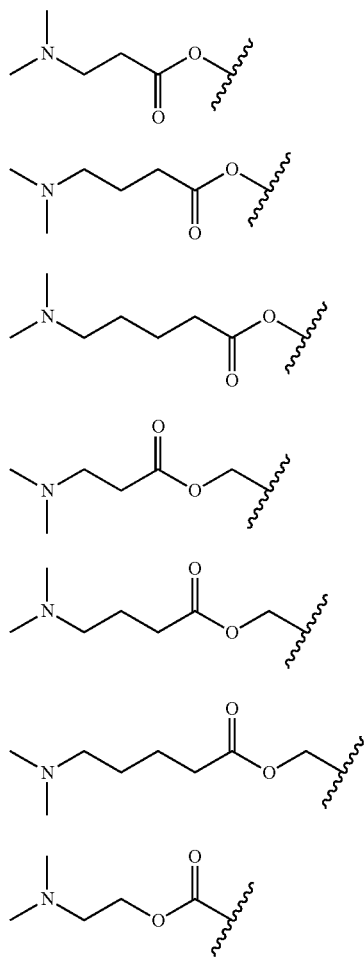
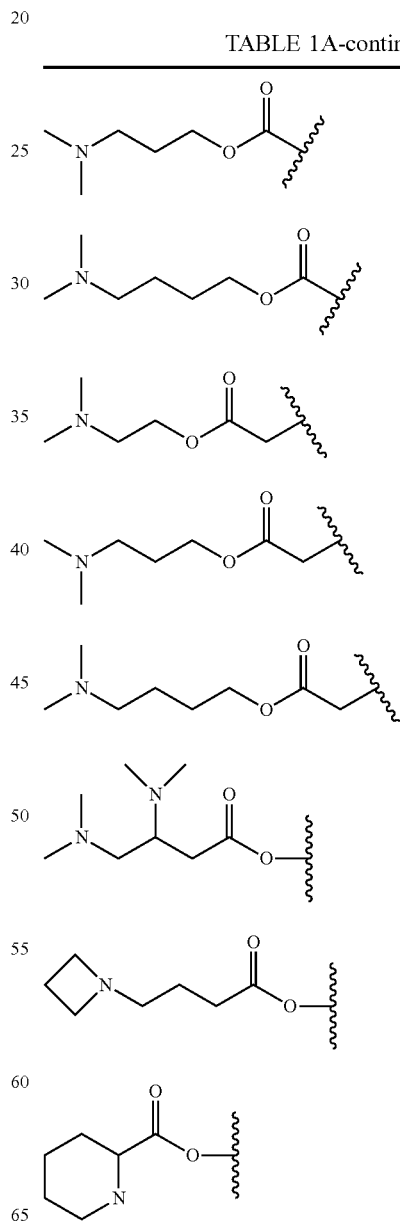


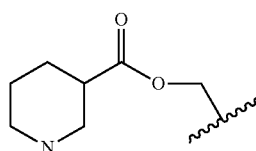
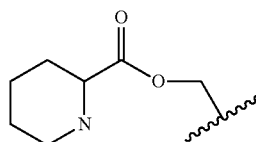
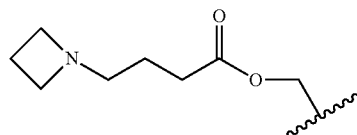
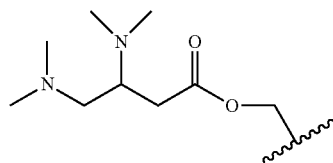
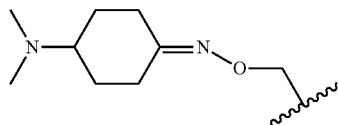
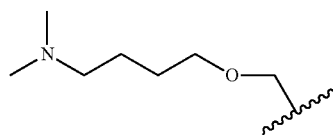
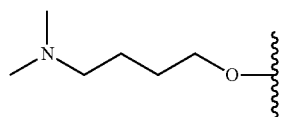
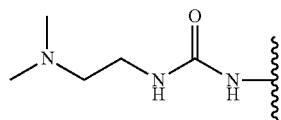
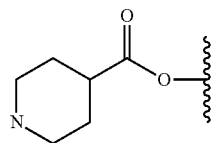
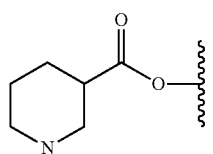
TABLE 1A-continued



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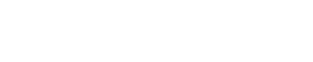
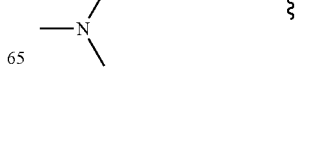
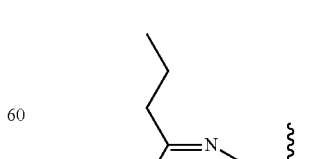
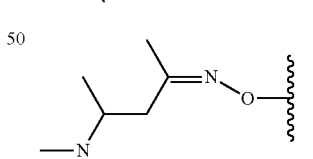
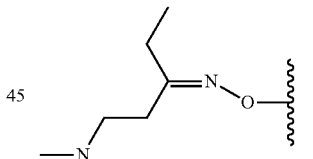
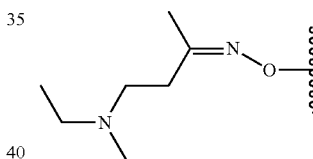
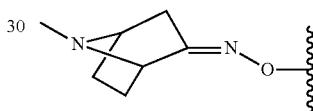
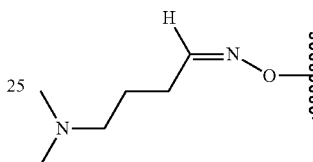
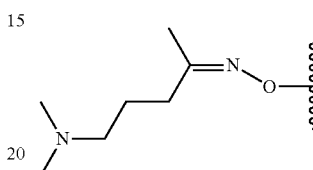
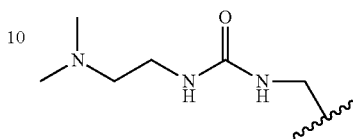
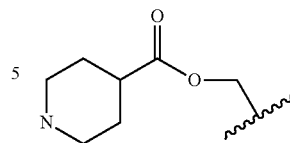
39

TABLE 1A-continued



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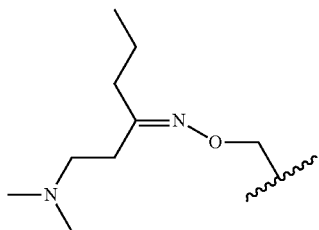
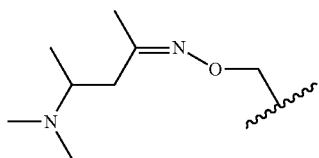
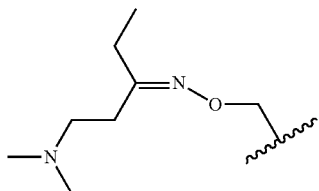
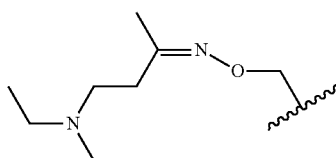
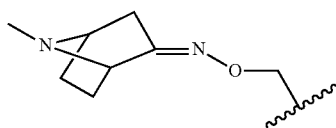
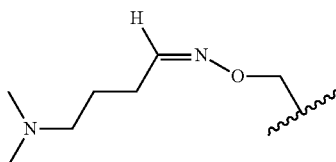
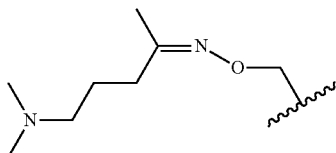
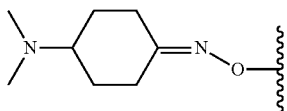
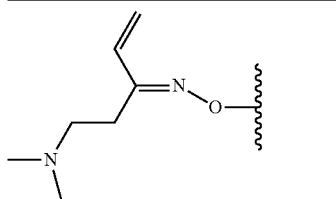
TABLE 1A-continued



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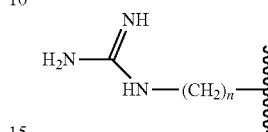
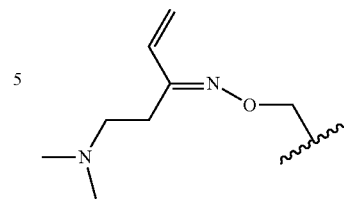
41

TABLE 1A-continued

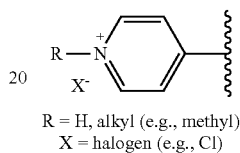


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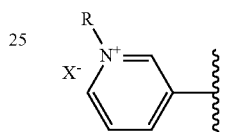
TABLE 1A-continued



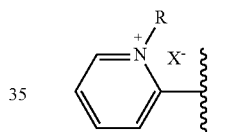
(where n is 0-5)



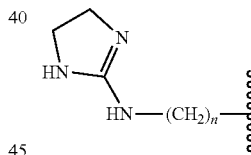
R = H, alkyl (e.g., methyl)
X = halogen (e.g., Cl)



30 R = H, alkyl (e.g., methyl)
X = halogen (e.g., Cl)



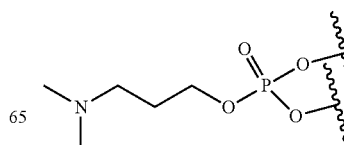
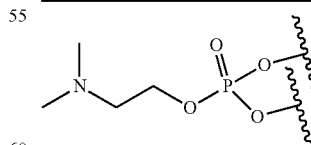
R = H, alkyl (e.g., methyl)
X = halogen (e.g., Cl)



(where n is 0-5)

Suitable primary groups include, but are not limited to, those that are a combination of a head group from table 1A with a central carbon atom. Other suitable primary groups include those in table 1B below:

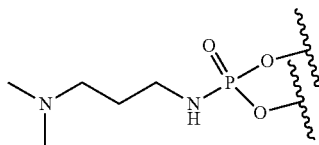
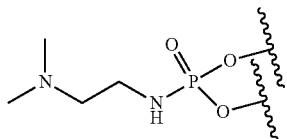
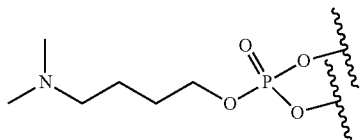
TABLE 1B



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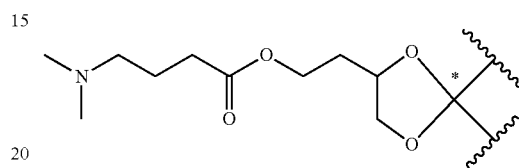
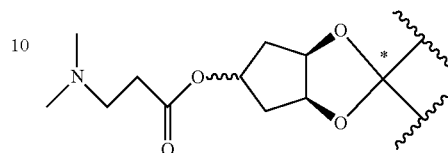
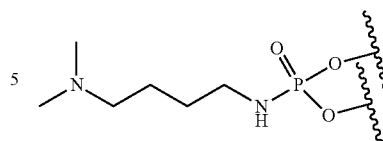
43

TABLE 1B-continued



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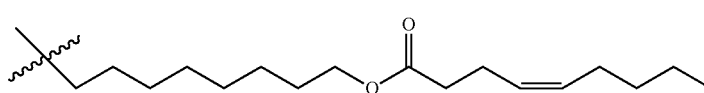
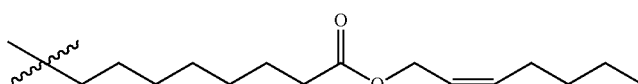
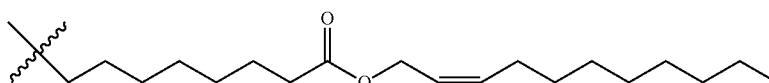
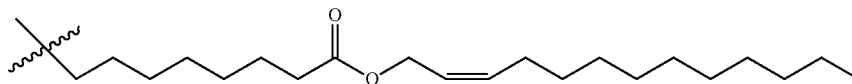
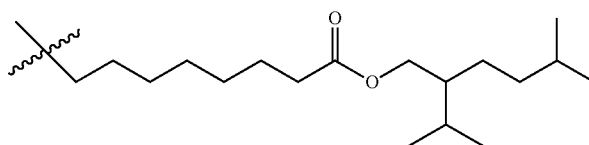
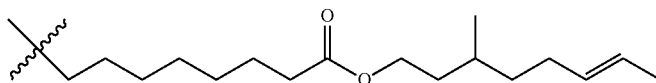
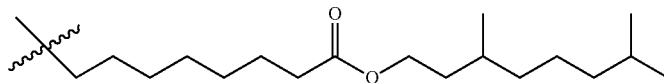
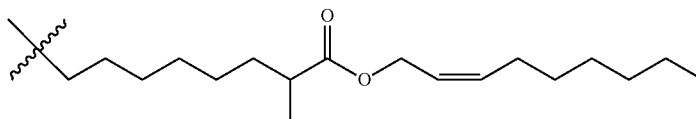
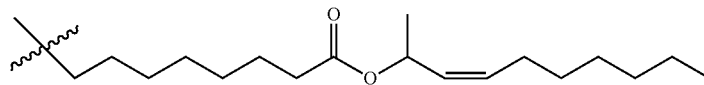
TABLE 1B-continued



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Some suitable hydrophobic tail groups include those depicted in Table 1C:

TABLE 1C

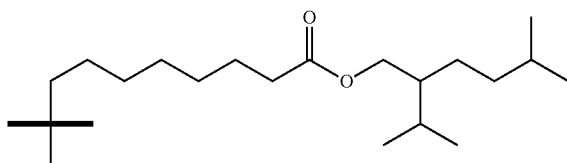
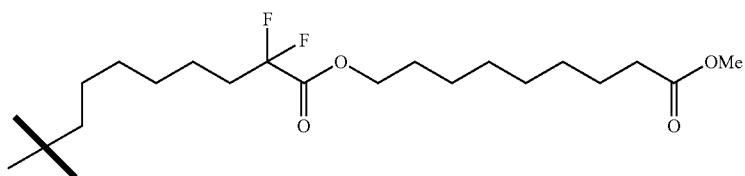
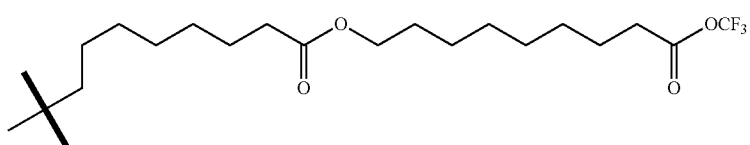
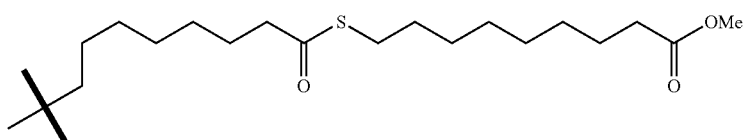
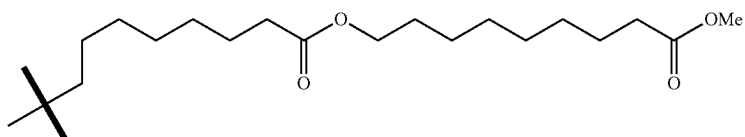
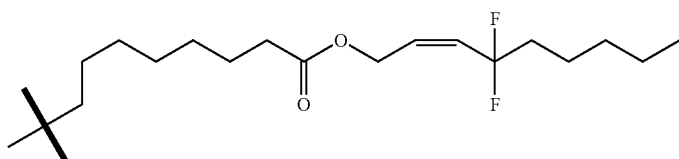
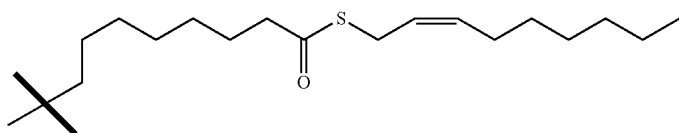
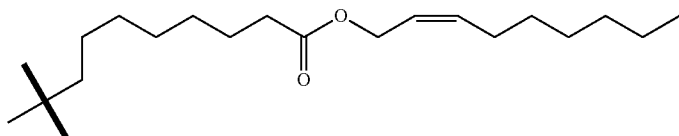
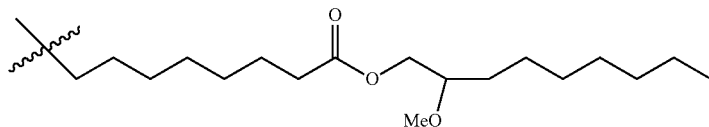
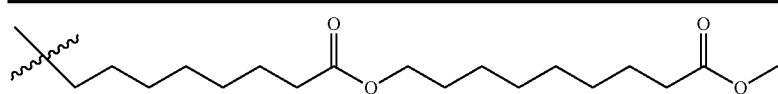


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TABLE 1C-continued

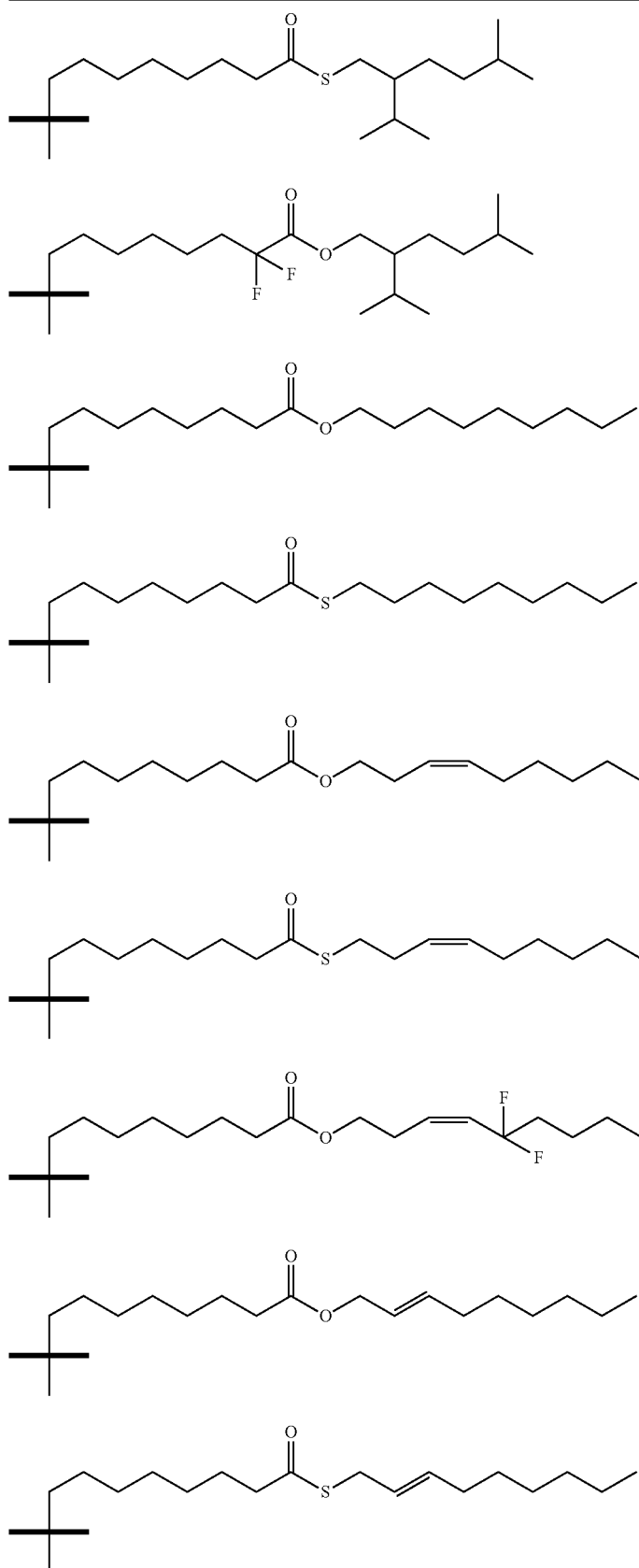


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TABLE 1C-continued

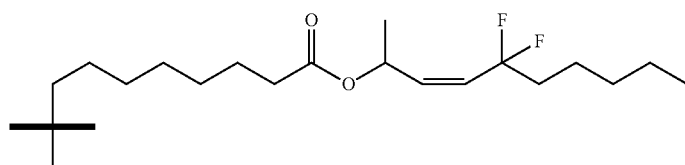
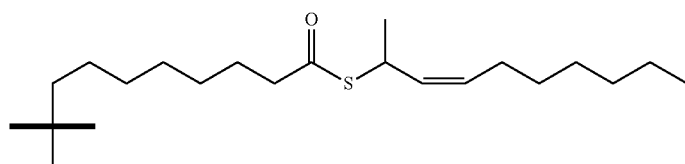
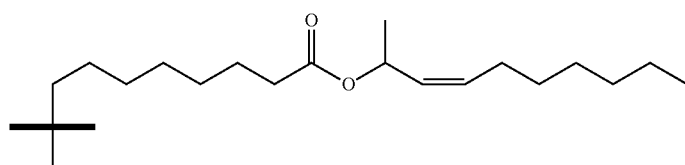
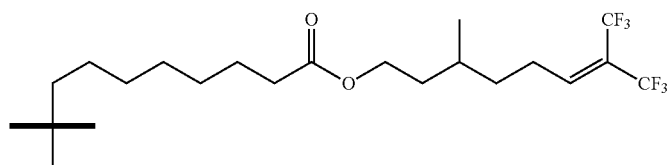
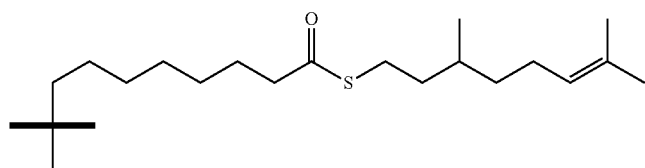
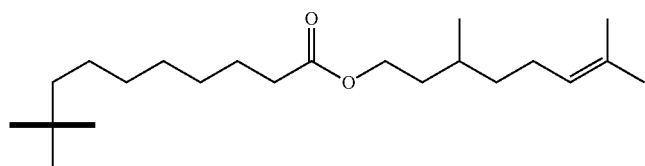
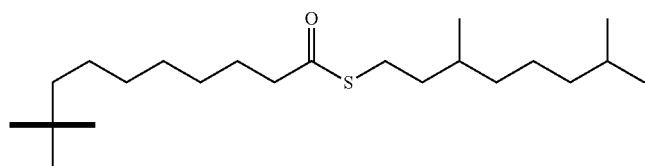
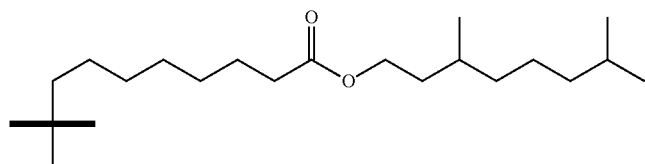
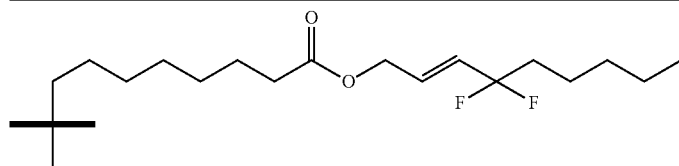


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TABLE 1C-continued

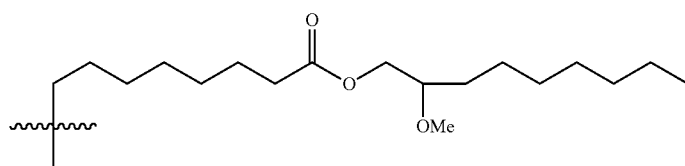
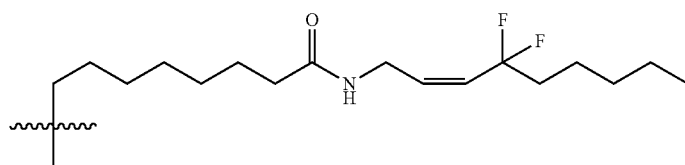
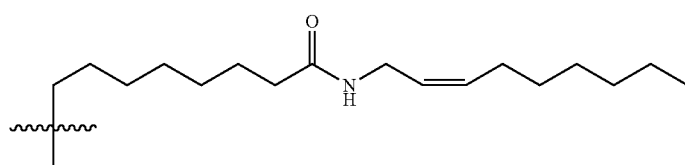
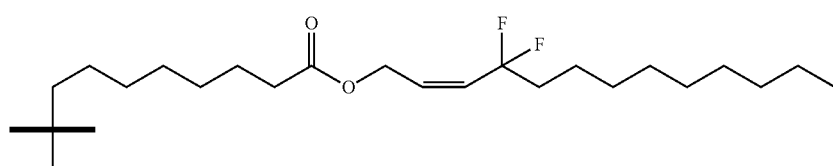
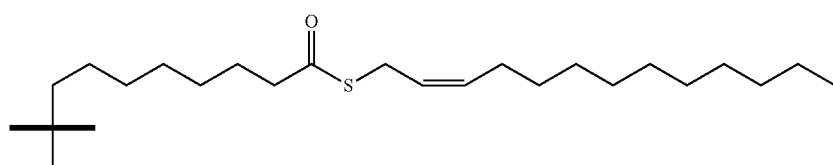
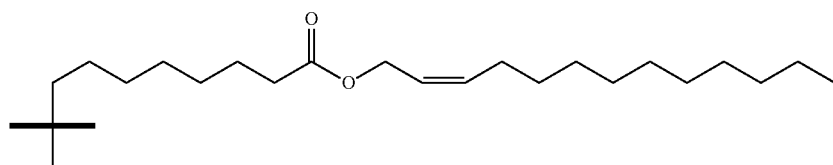
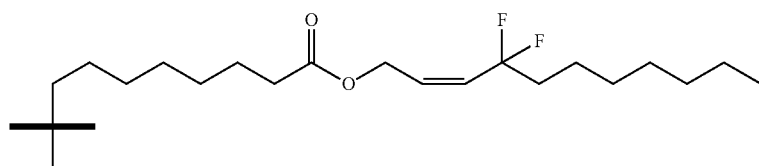
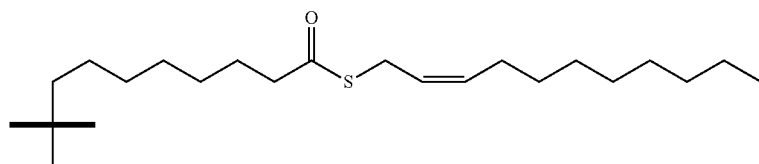
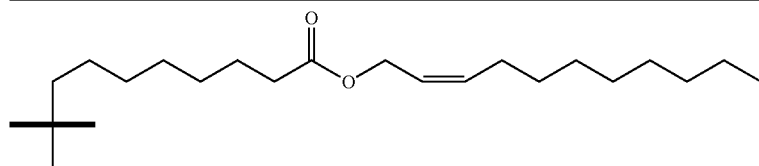


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TABLE 1C-continued



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TABLE 1C-continued

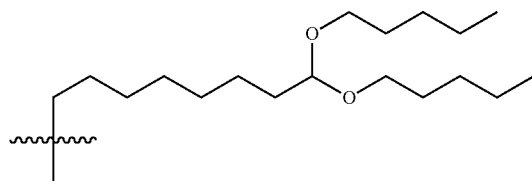
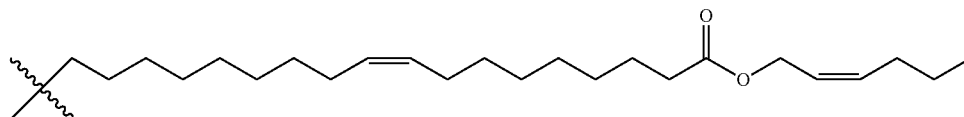
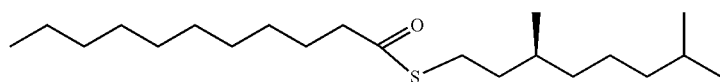
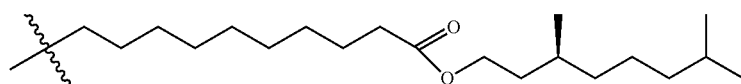
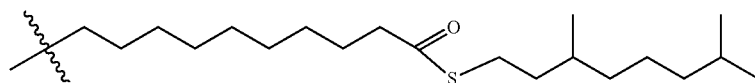
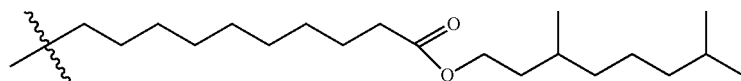
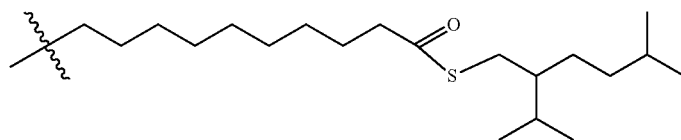
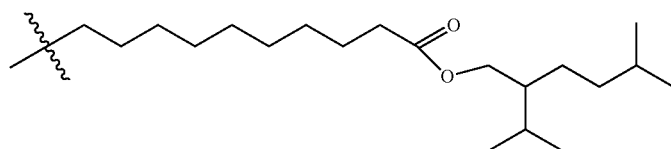
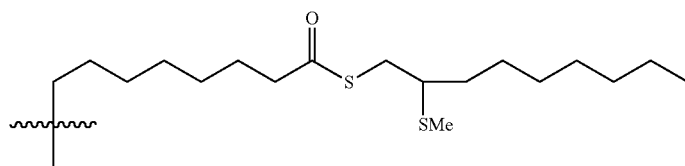
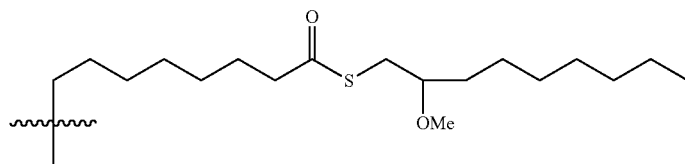
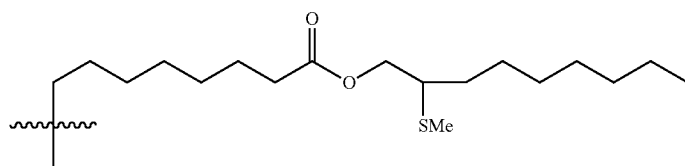
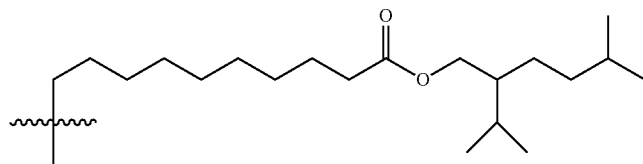


TABLE 1C-continued



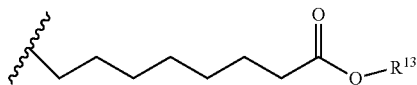
10

Other suitable tail groups includes those of the formula $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ where R^{12} is a $\text{C}_4\text{—C}_{14}$ alkyl or $\text{C}_4\text{—C}_{14}$ alkenyl, M^1 is a biodegradable group as defined above, and R^{13} is a branched alkyl or alkenyl (e.g., a $\text{C}_{10}\text{—C}_{20}$ alkyl or $\text{C}_{10}\text{—C}_{20}$ alkenyl), such that (i) the chain length of $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ is at most 21 atoms (i.e., the total length of the tail from the first carbon after the tertiary carbon (marked with an asterisk) to a terminus of the tail is at most 21), and (ii) the group $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ has at least 20 carbon atoms (e.g., at least 21 or 22 carbon atoms).

In one preferred embodiment, the chain length of $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ is at most 21 (e.g., at most 20). For example, the chain length can be from about 17 to about 24 or from about 18 to about 20.

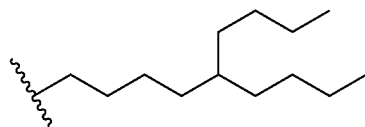
In one embodiment, the total carbon atom content of each tail ($\text{—R}^{12}\text{—M}^1\text{—R}^{13}$) is from about 17 to about 26. For example, the total carbon atom content can be from about 19 to about 26 or from about 21 to about 26.

In one embodiment, the tail has the formula:

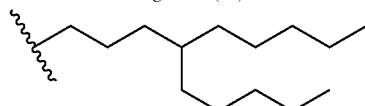


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where R^{13} is an alkyl or alkenyl group having from about 13 to about 17 carbon atoms, and the total carbon length of the tail from the first carbon (the leftmost carbon atom above) to a terminus of the tail is at most 20. Preferably, the tail has from about 22 to about 26 carbon atoms. In one embodiment, the maximum length of R^{13} from its attachment point to the ester group of the compound is 12 carbon atoms (e.g., the maximum length can be 11 carbon atoms). In one preferred embodiment, the branch in the alkyl or alkenyl group is at the δ -position or later from the point of attachment of R^{13} to the ester group. Suitable R^{13} groups include, but are not limited to



C13 (C21)
Length: C9 (18)



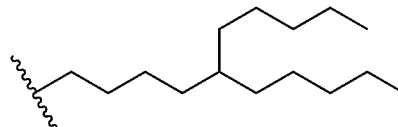
C14 (C22)
Length: C9 (18)

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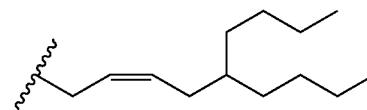
60

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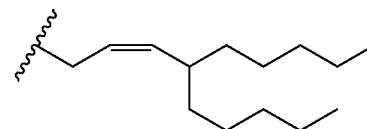
-continued



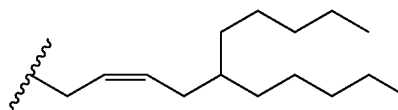
C15 (C23)
Length: C10 (19)



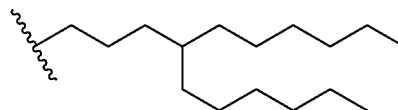
C13 (C21)
Length: C9 (18)



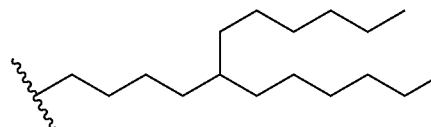
C14 (C22)
Length: C9 (18)



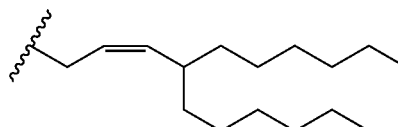
C15 (C23)
Length: C10 (19)



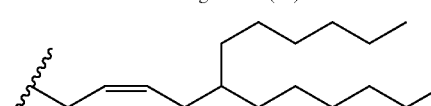
C16 (C24)
Length: C10 (19)



C17 (C25)
Length: C11 (20)



C16 (C24)
Length: C10 (19)

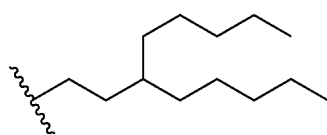
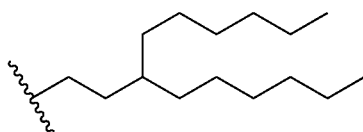


C17 (C25)
Length: C11 (20)

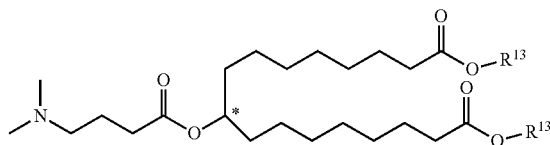
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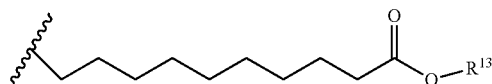
C13 (C21)
Length: C8 (17)C15 (C23)
Length: C9 (18)

For example, the cationic lipid can be

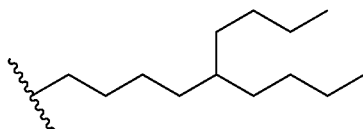


or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), where R^{13} is selected from the groups mentioned above.

Another example is a tail of the formula

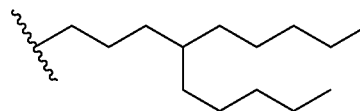
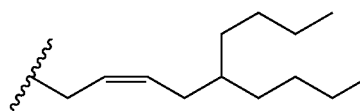
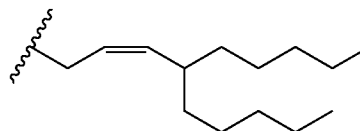
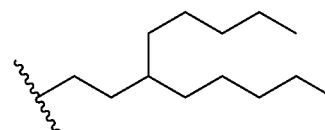


where R^{13} is an alkyl or alkenyl group having from about 13 to about 15 carbon atoms, and the total carbon length of the tail from the first carbon (i.e., the leftmost carbon atom, which is attached to a tertiary carbon) to a terminus of the tail is at most 20. Preferably, the tail has from about 24 to about 26 carbon atoms. In one embodiment, the maximum length of R^{13} from its attachment point to the ester group of the compound is 10 carbon atoms (e.g., the maximum length can be 9 carbon atoms). In one preferred embodiment, the branch in the alkyl or alkenyl group is at the δ -position or later from the point of attachment of R^{13} to the ester group. Suitable R^{13} groups include, but are not limited to

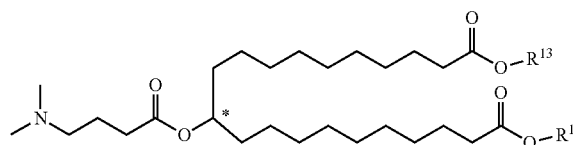
C13 (C23)
Length: C9 (20)

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-continued

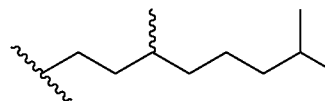
C14 (C24)
Length: C9 (20)C13 (C23)
Length: C9 (20)C14 (C24)
Length: C9 (20)C13 (C24)
Length: C8 (19)

For example, the cationic lipid can be



or a salt thereof (e.g., a pharmaceutically acceptable salt thereof), where R^{13} is selected from the groups above.

The R^{13} group may be derived from a natural product, such as dihydrocitronellol, lavandulol, phytol, or dihydrophytol. In one embodiment, the R^{13} group in the tails above is a dihydrocitronellol group (either as a racemic group or a chirally pure group):

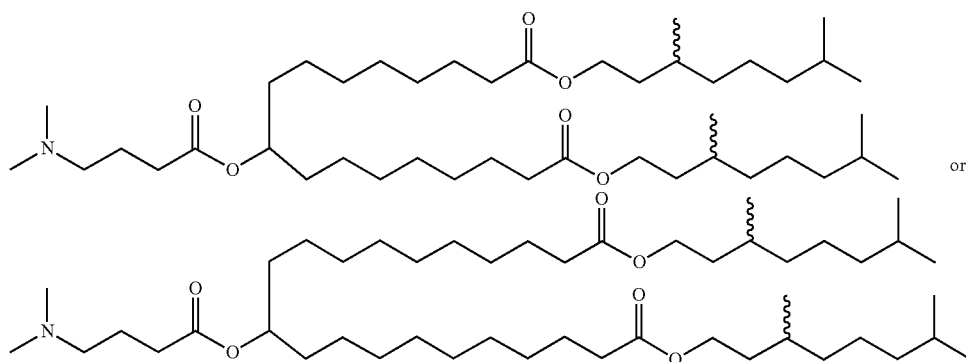


For example, the cationic lipid having a dihydroitronellol group can be

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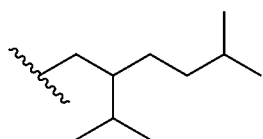
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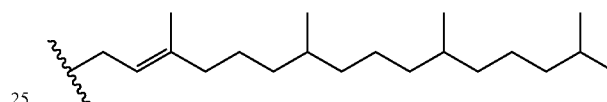
or a salt thereof.

In another embodiment, the R¹³ group in the tails above is a lavandulol group or a homolog of it as shown below: 20

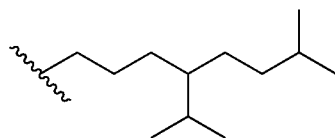
In another embodiment, the R¹³ group in the tails above is a phytol or dihydro phytol group:



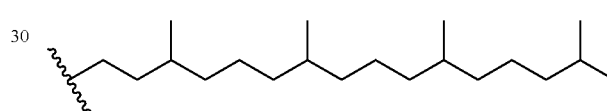
Lavandulol



Phytol

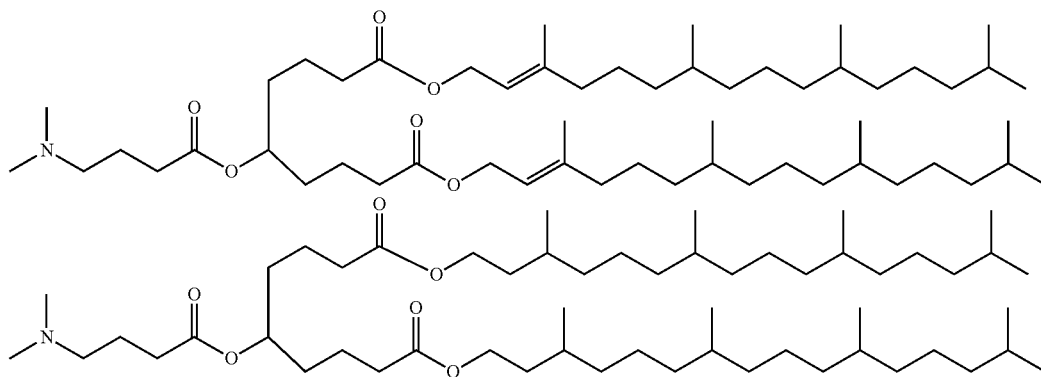


homolog

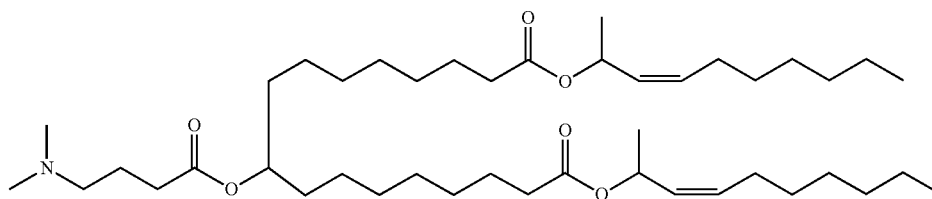


Dihydrophytol

For instance, the cationic lipid can be:



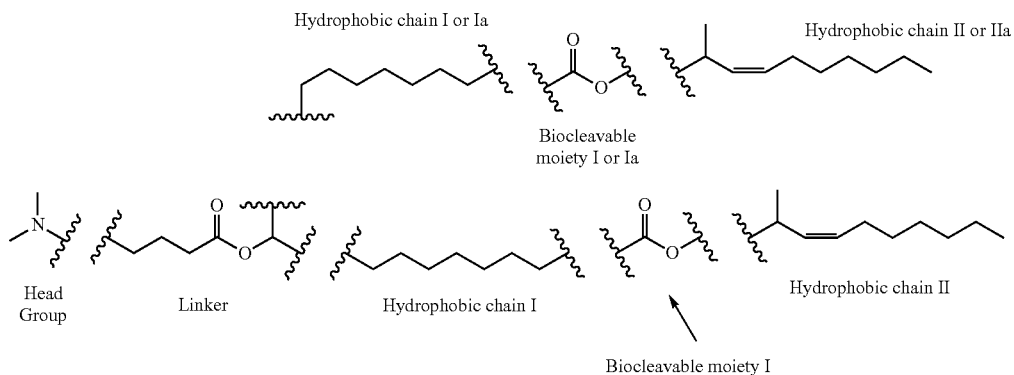
A cationic lipid of the formula:



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can also be thought of as a combination of a headgroup, a linker moiety, and two parts of the hydrophobic chains as follows:



Various headgroups, linker moieties, and hydrophobic chains I and II are listed below. The present invention includes compounds composed of any combination of the head, linker, hydrophobic chain I, and hydrophobic chain II groups listed below.

TABLE 2A

Representative headgroups

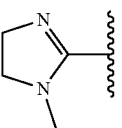
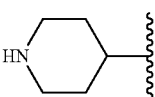
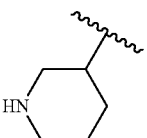
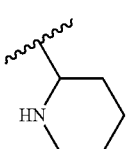
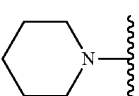
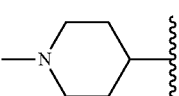
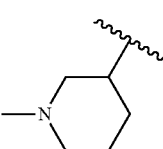
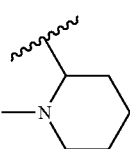
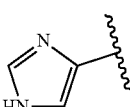
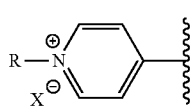
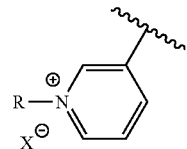
TABLE 2A-continued

Representative headgroups
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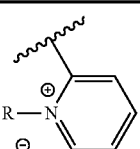
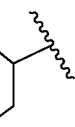
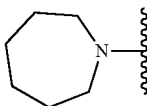
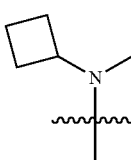
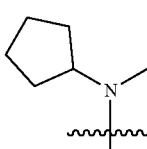
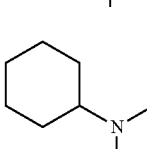
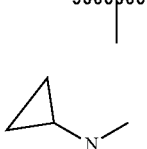

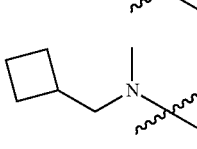
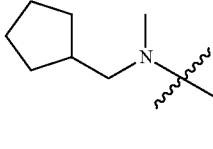

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TABLE 2A-continued

Representative headgroups










R = H, alkyl; X = halogen

R = H, alkyl; X = halogen

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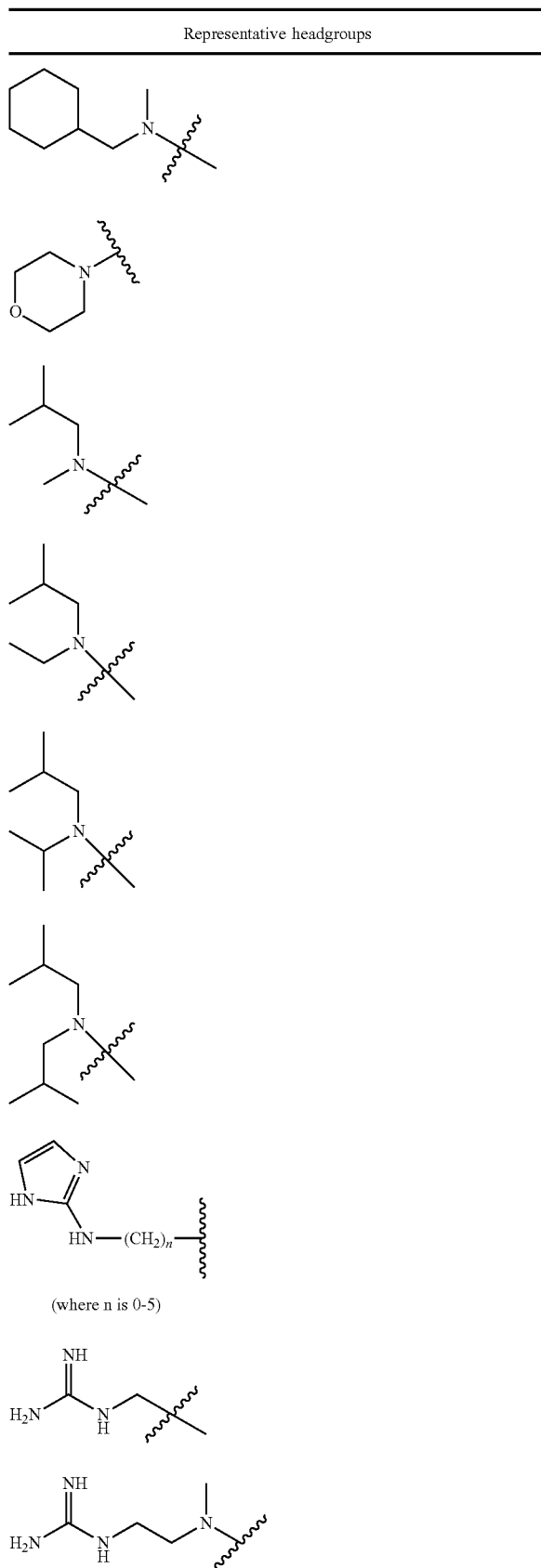
TABLE 2A-continued

Representative headgroups
5 
10 R = H, alkyl; X = halogen
15 
20 
25 
30 
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40 
45 
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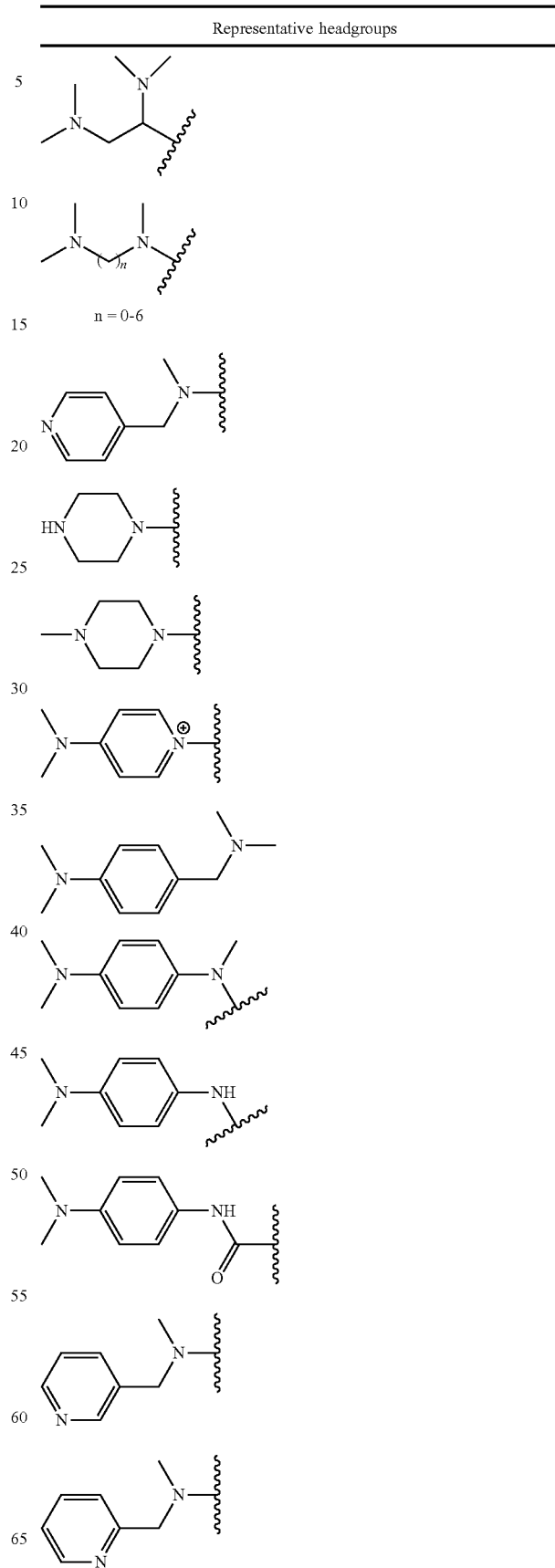
65

TABLE 2A-continued



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TABLE 2A-continued



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TABLE 2A-continued

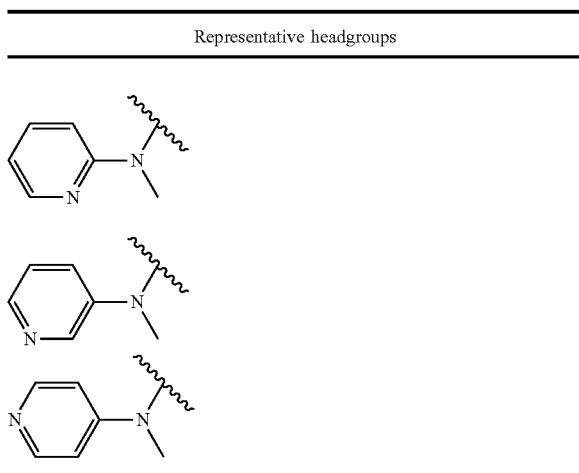
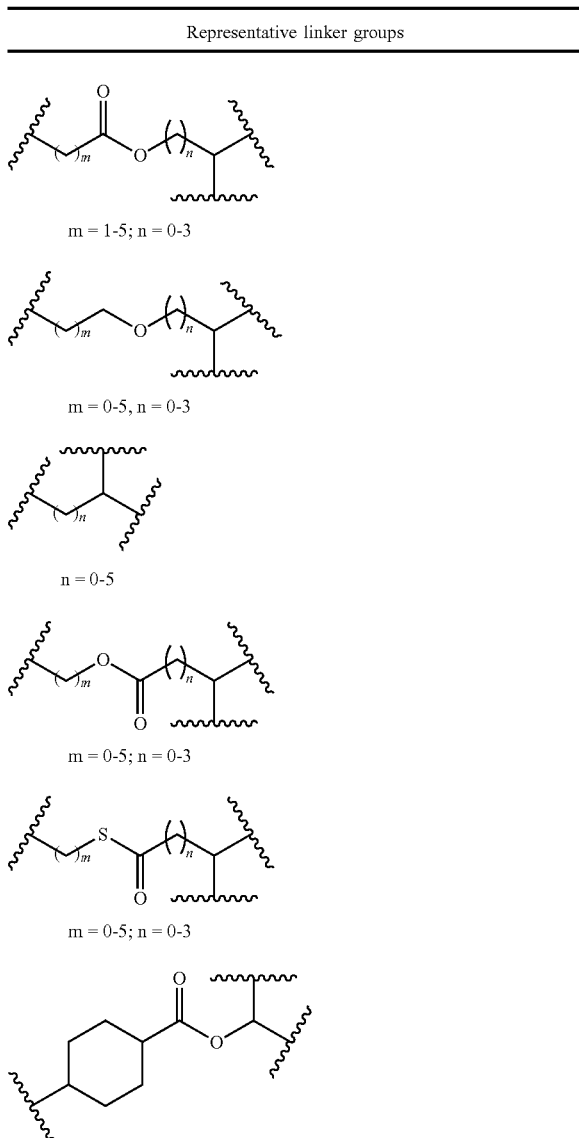
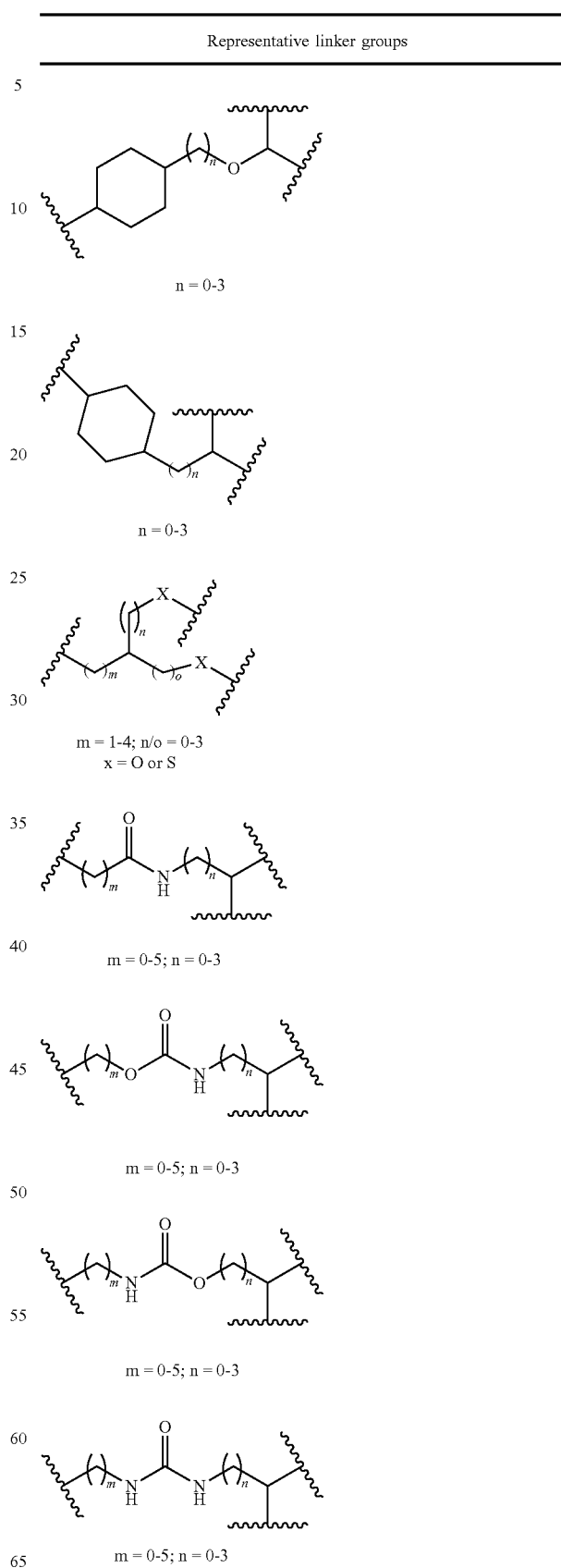


TABLE 2B



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TABLE 2B-continued

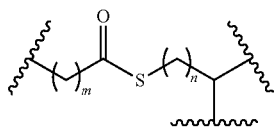


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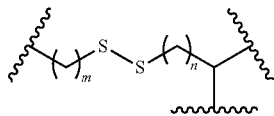
69

TABLE 2B-continued

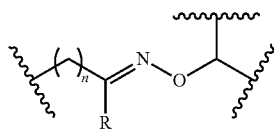
Representative linker groups



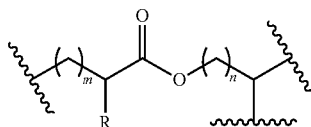
m = 0-5; n = 0-3



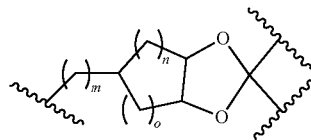
m = 0-5; n = 0-3



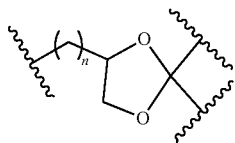
n = 0-5



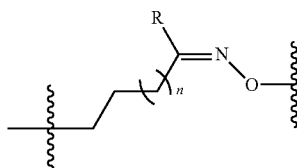
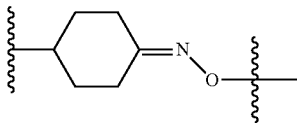
m = 1-4; n = 0-3
R = COOH, COOME, COOEt,
CN, CONH₂, CONHMe



m = 1-4; n/o = 1-3



n = 1-5

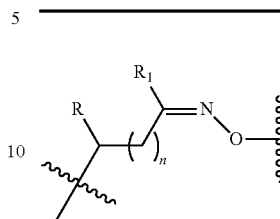


R = H, Me, Et, Pr, allyl

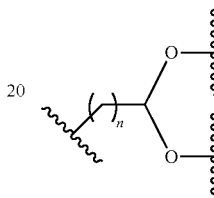
70

TABLE 2B-continued

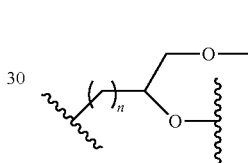
Representative linker groups



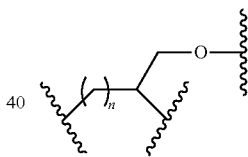
R = Me, Et, Pr, allyl
R₁ = Me, Et, Pr, allyl



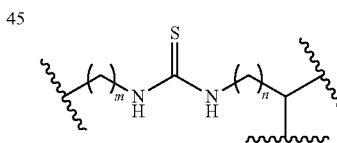
n = 0-6



n = 0-6



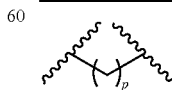
n = 0-6



m = 0-5; n = 0-3

TABLE 2C

Representative hydrophobic
chain I and/or Ia, and combination thereof

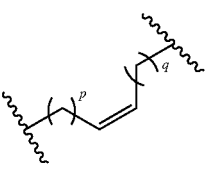
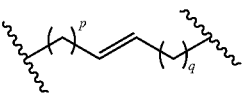
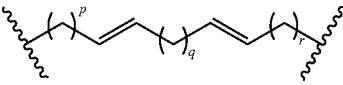
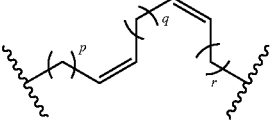
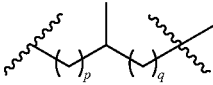
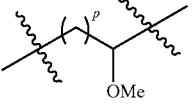
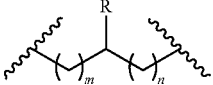
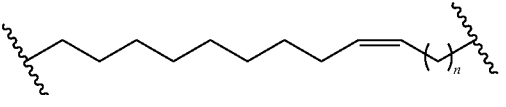
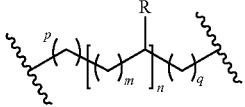


p = 0-15

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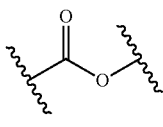
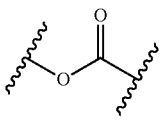
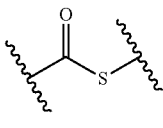
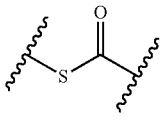
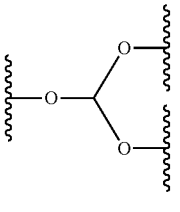
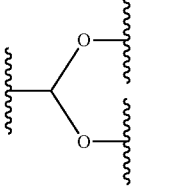
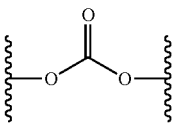
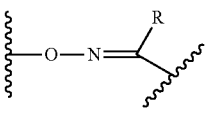
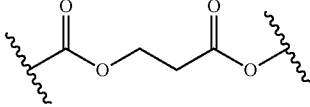
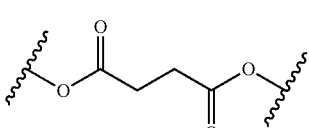

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TABLE 2C-continued

Representative hydrophobic chain I and/or Ia, and combination thereof	
	
p = 0-15, q = 0-15	
	
p = 0-15, q = 0-15	
	
p = 0-15, q = 1-4, r = 0-15	
	
p = 0-15, q = 1-4, r = 0-15	
	
p = 0-15, q = 0-6	
	
p = 0-15	
	
m = 0-4; n = 0-4; R = Me, Et, Pr, iPr, Bu, iBu	
	
n = 1-7	
	
m = 1-4, n = 1-10, p = 0-15, q = 0-15 R = Me, Et, OMe	

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TABLE 2D

Representative biodegradable moieties I and/or Ia and combinations thereof	
5	
10	
15	
20	
25	
30	
35	
40	
45	
50	
55	
60	
65	

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TABLE 2D-continued

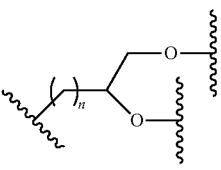
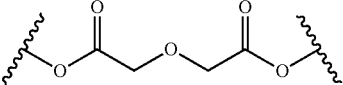
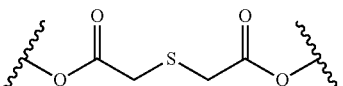
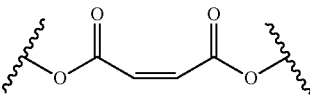
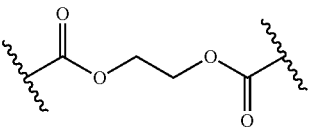
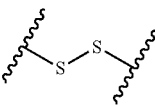
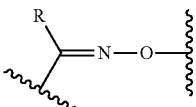
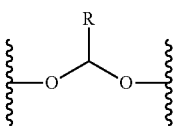
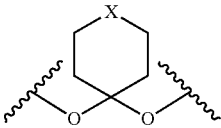
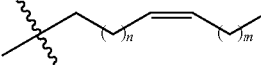
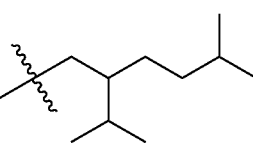
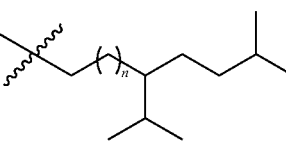
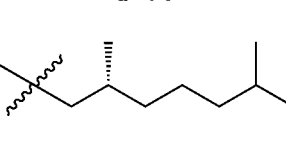
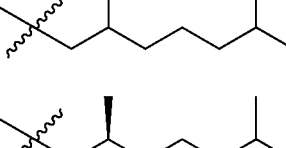
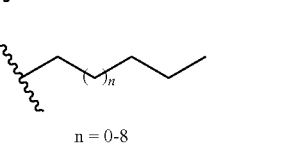
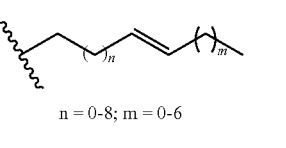
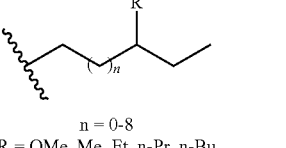
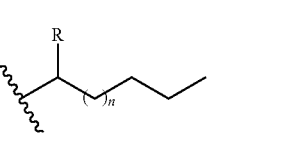
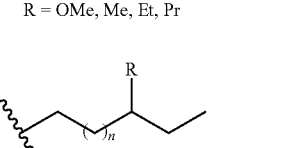
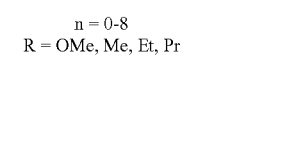

Representative biodegradable moieties I and/or Ia and combinations thereof
 <p>$n = 0-6$</p>






 <p>R = H, Me, Et, cyclic alkyl, alicyclic, aromatic</p>
 <p>X = CH₂, O, S</p>

TABLE 2E

Representative hydrophobic chain II and/or IIa and combinations thereof
 <p>$n = 0-6; m = 0-16$</p>

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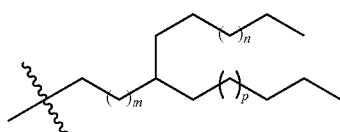
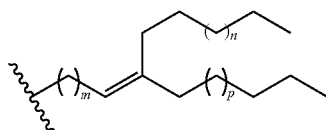
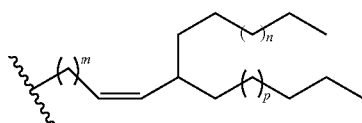
TABLE 2E-continued

Representative hydrophobic chain II and/or IIa and combinations thereof
 <p>5</p>
 <p>10</p>
 <p>15</p> <p>$n = 0-6$</p>
 <p>20</p>
 <p>25</p>
 <p>30</p>
 <p>35</p> <p>$n = 0-8$</p>
 <p>40</p> <p>$n = 0-8; m = 0-6$</p>
 <p>45</p> <p>$n = 0-8$ R = OMe, Me, Et, n-Pr, n-Bu</p>
 <p>50</p>
 <p>55</p> <p>$n = 0-8$ R = OMe, Me, Et, Pr</p>
<p>60</p> <p>$n = 0-8$ R = OMe, Me, Et, Pr</p>
<p>65</p>

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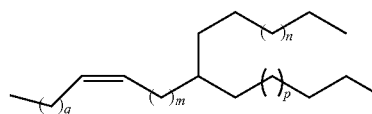
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TABLE 2E-continued

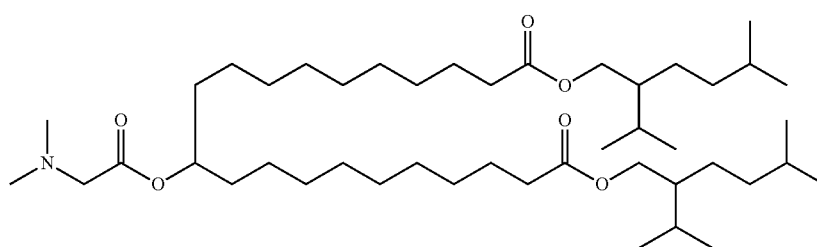
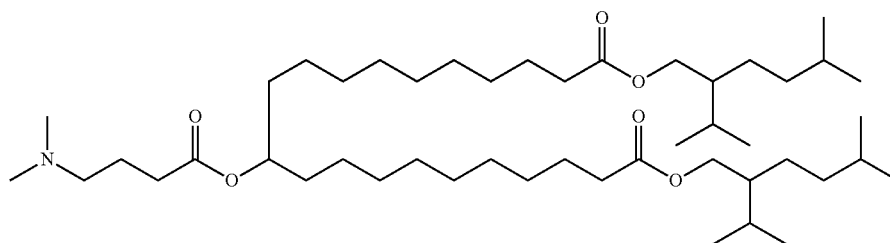
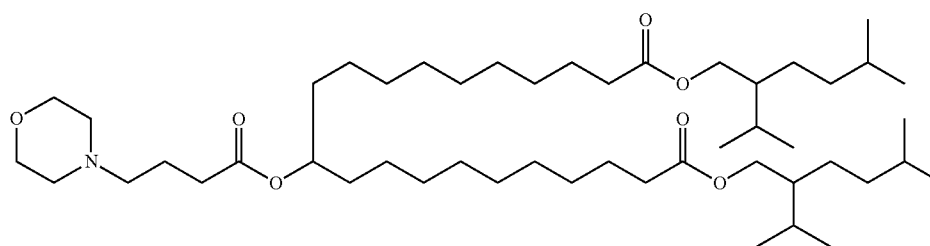
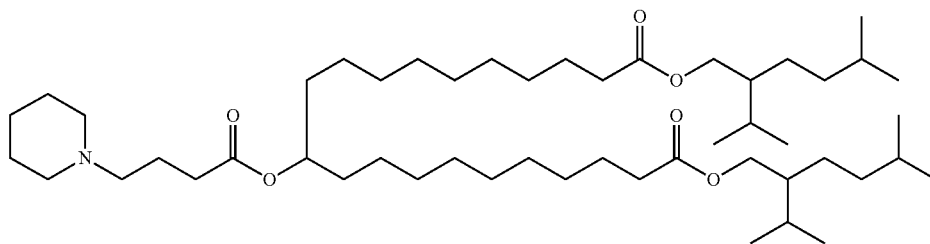
Representative hydrophobic
chain II and/or IIa and combinations thereof $m = 0-6; n = 0-6; p = 0-6$  $m = 0-6; n = 0-6; p = 0-6$  $m = 0-6; n = 0-6; p = 0-6$

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TABLE 2E-continued

Representative hydrophobic
chain II and/or IIa and combinations thereof $m = 0-6; n = 0-6; p = 0-6; q = 0-6$

Other cationic lipids of the present invention include those in Table 3 below. Each asymmetric carbon atom in the compounds below can be either chirally pure (R or S) or racemic. These cationic lipids as well as those in the working examples (such as Examples 36 and 37) are suitable for forming nucleic acid-lipid particles.

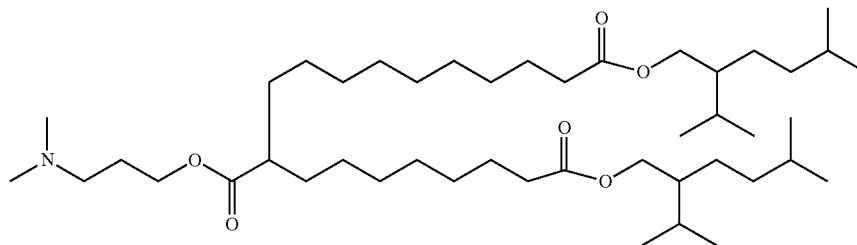
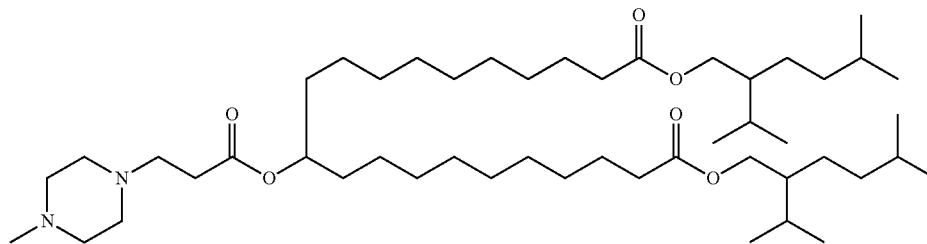
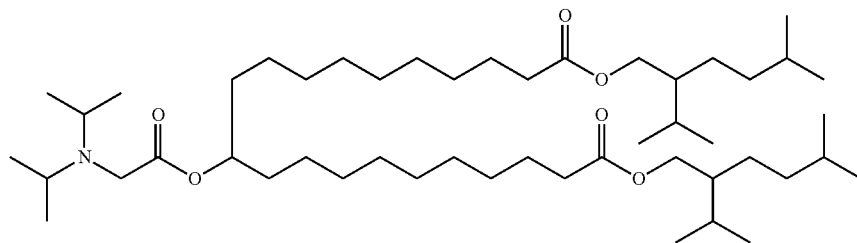
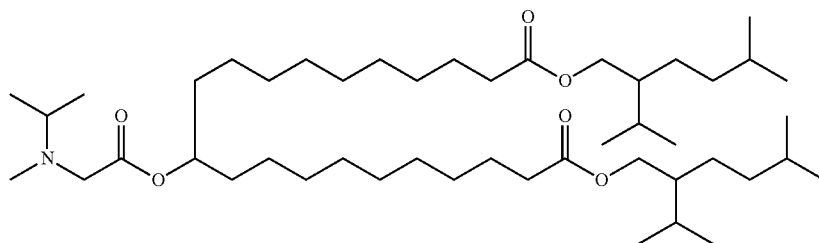
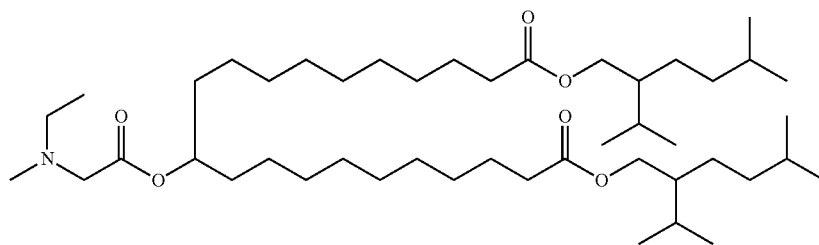
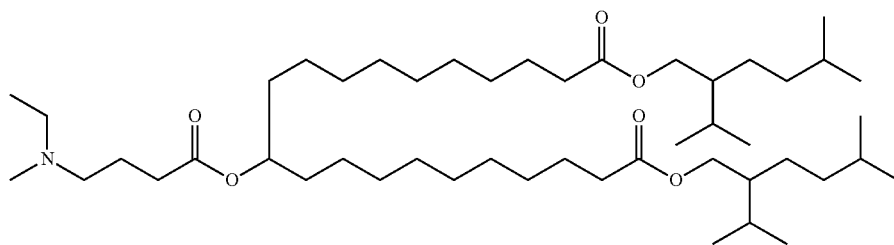


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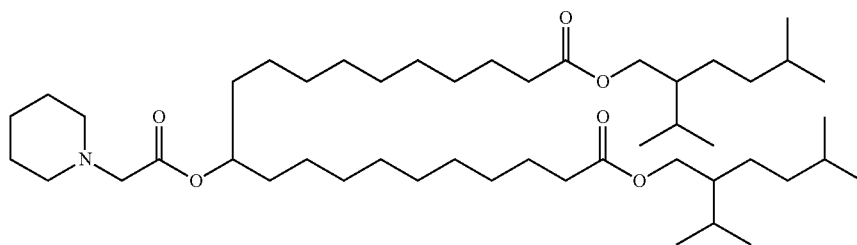
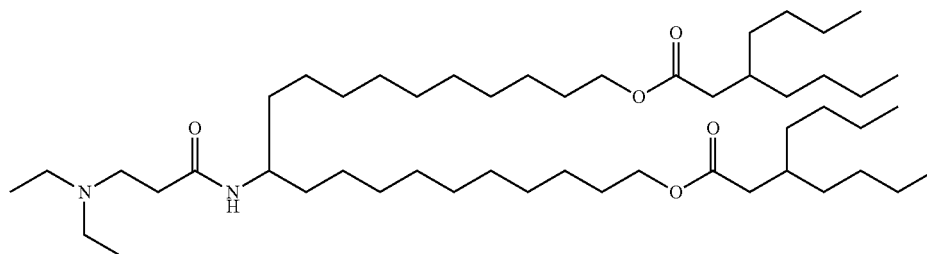
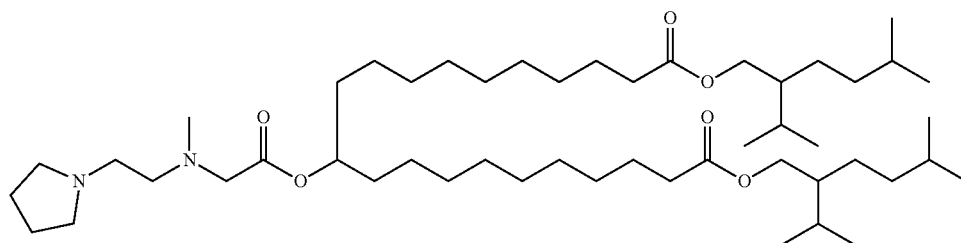
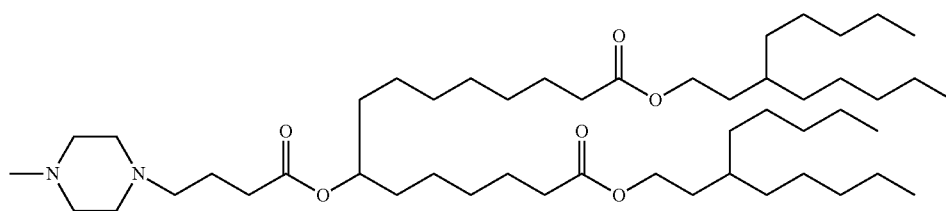
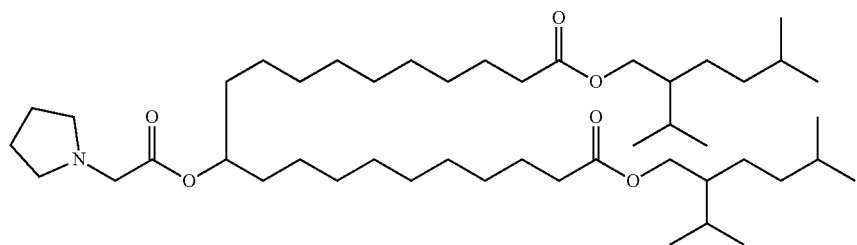
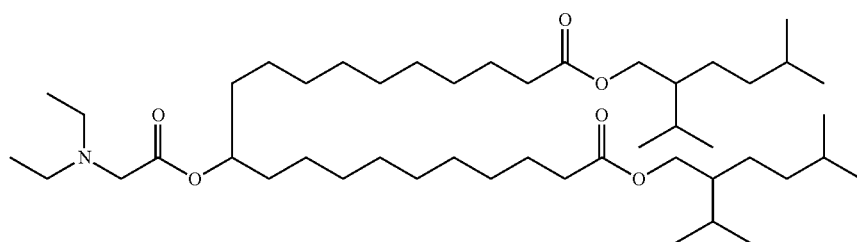


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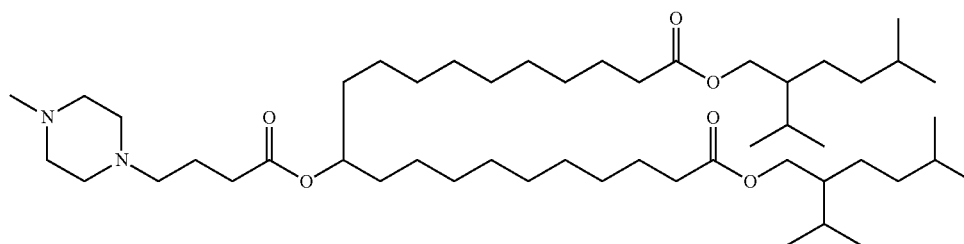
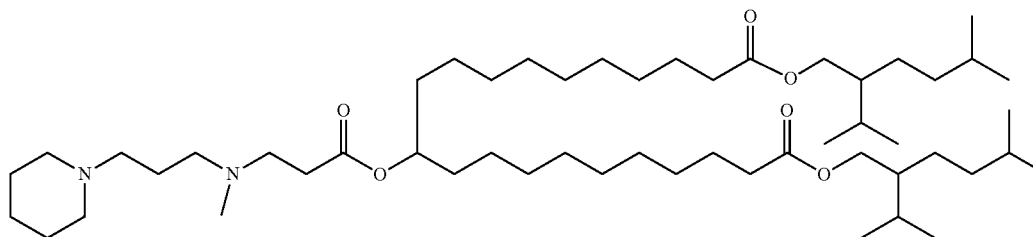
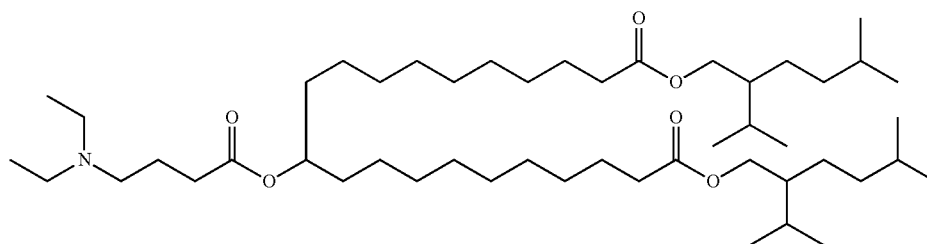
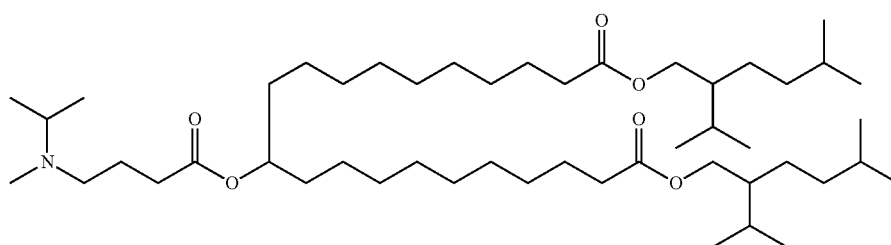
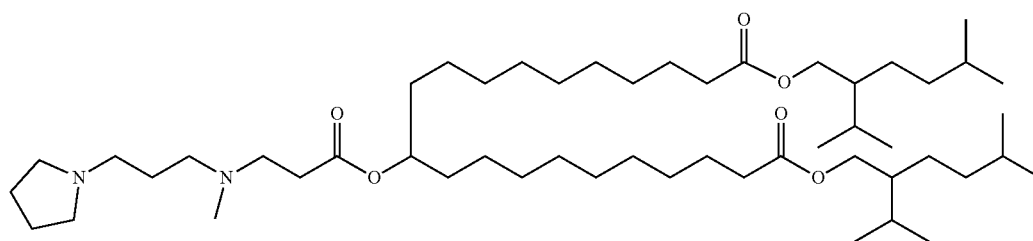
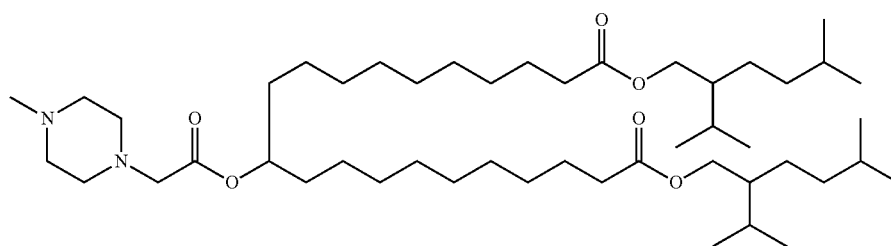


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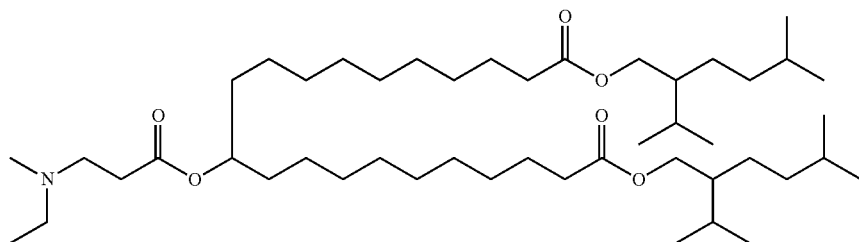
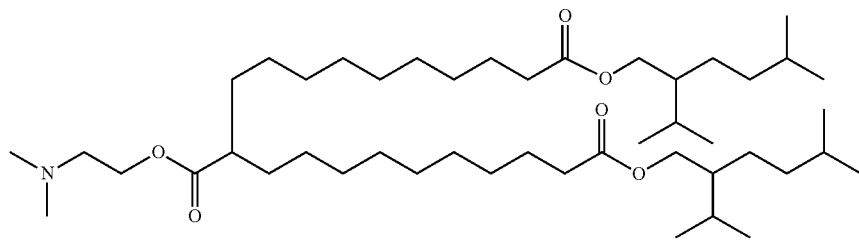
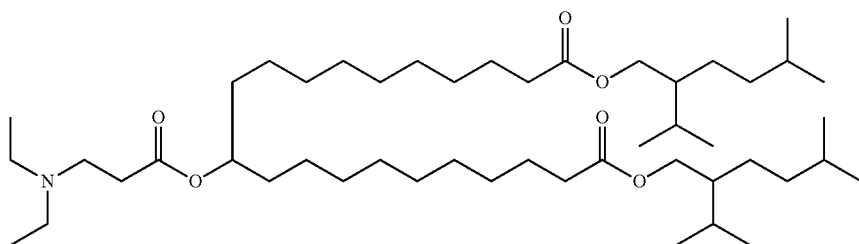
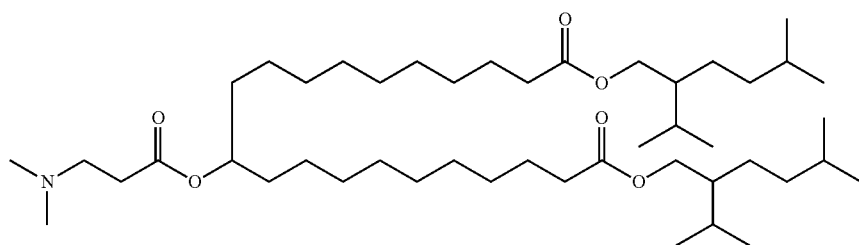
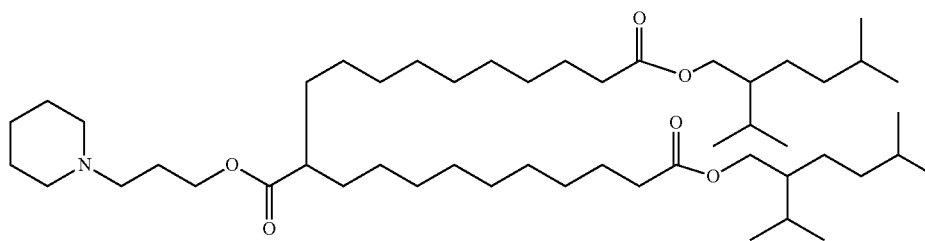
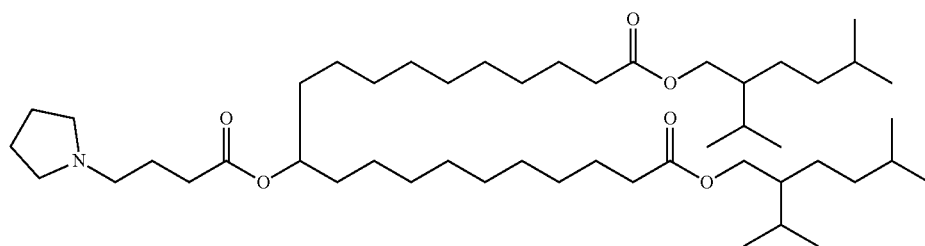


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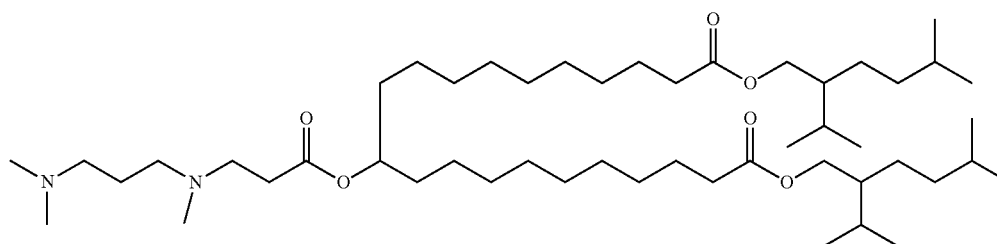
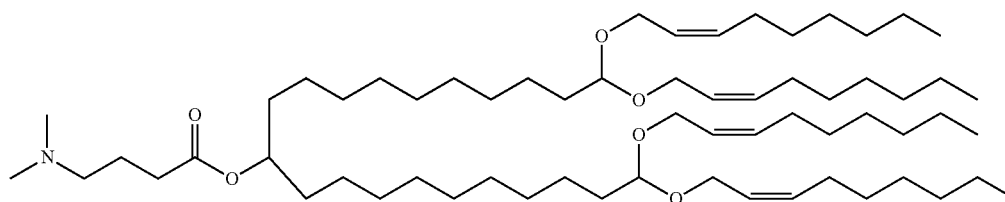
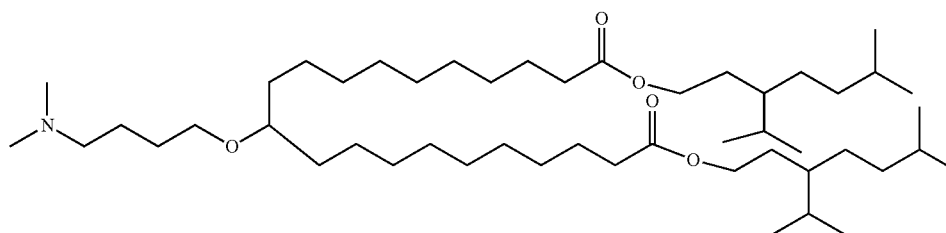
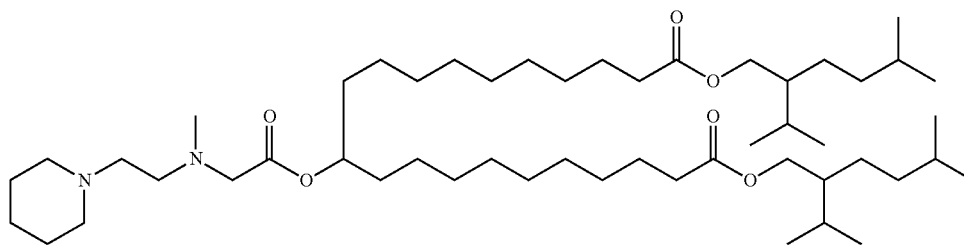
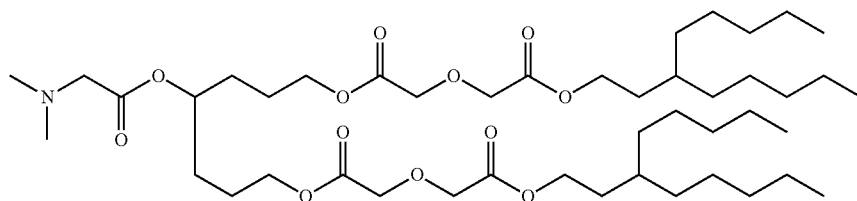
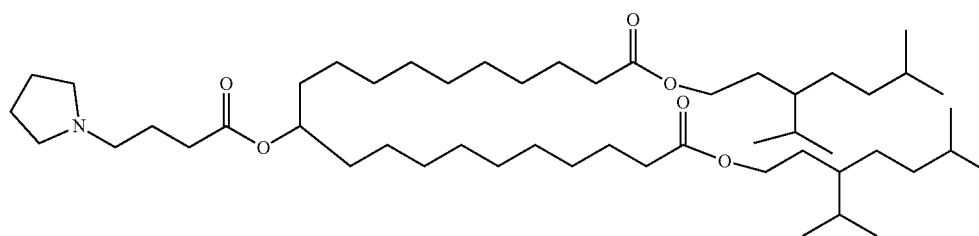
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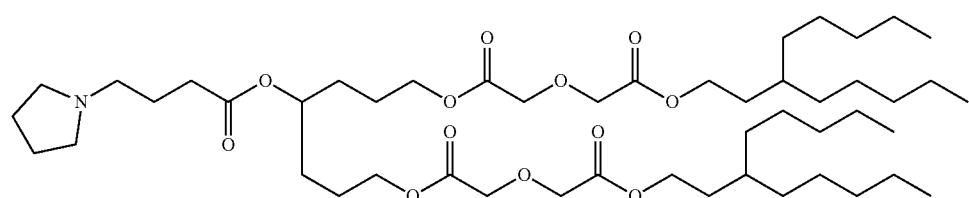
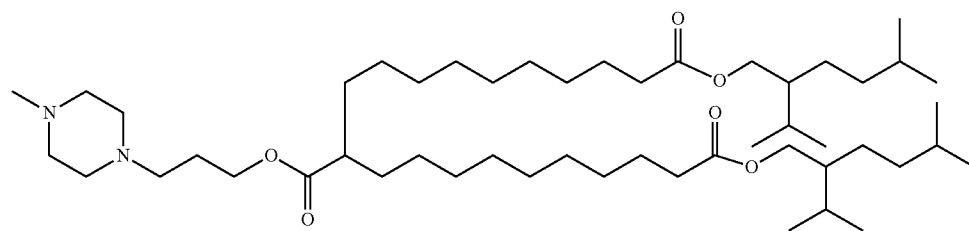
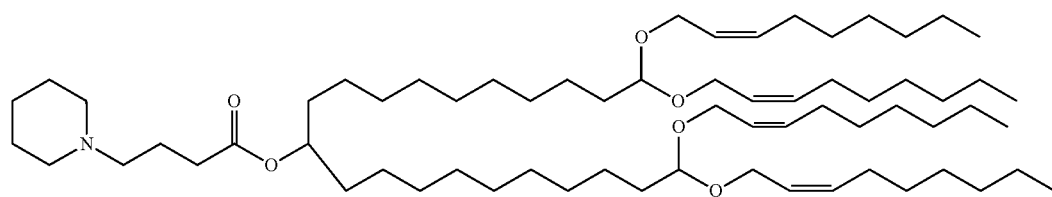
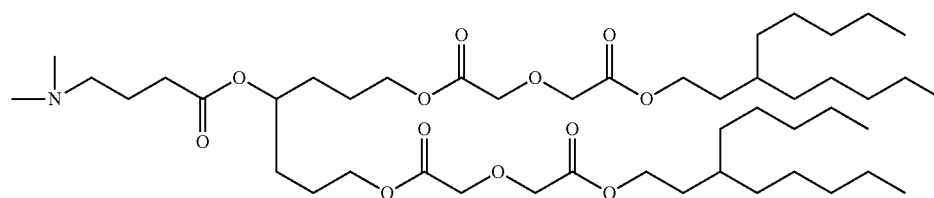
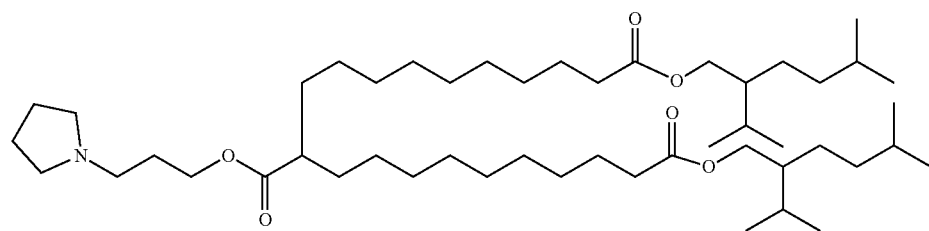
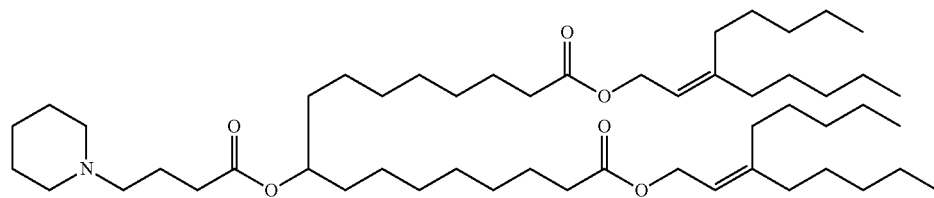
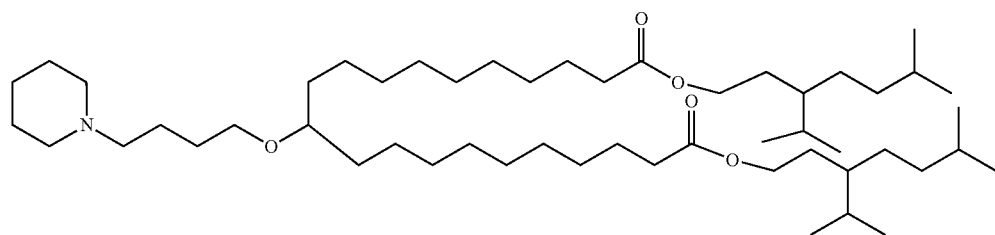


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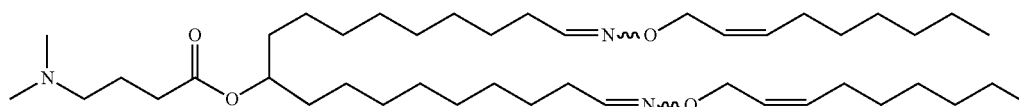
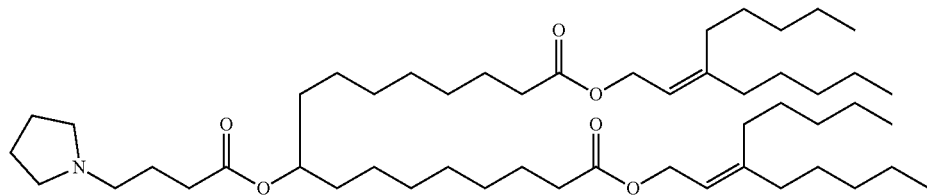
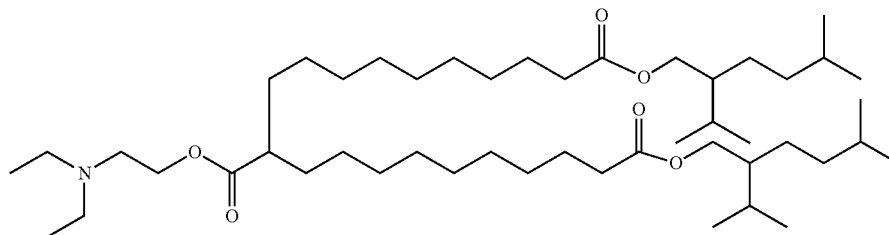
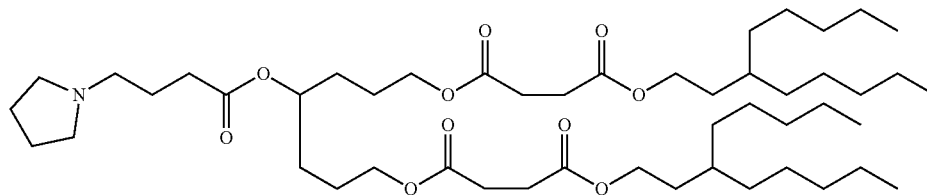
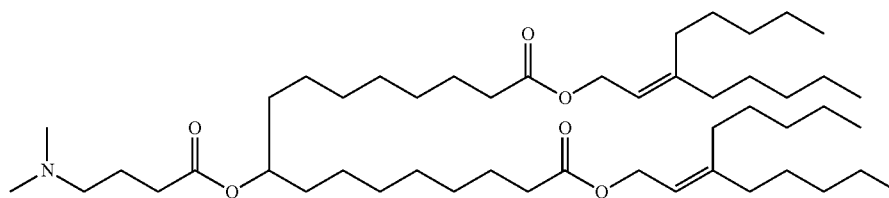
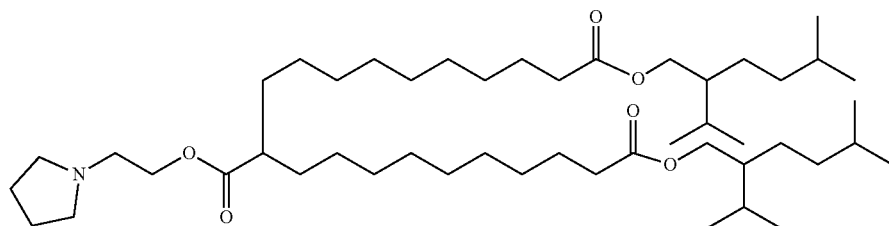
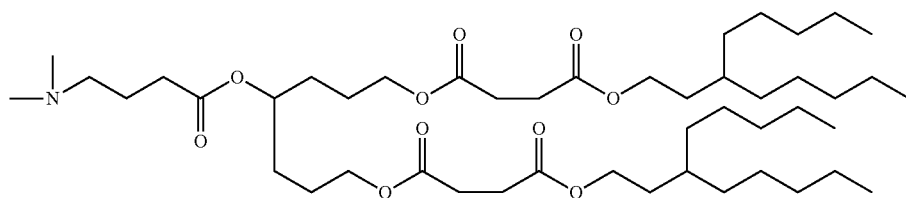


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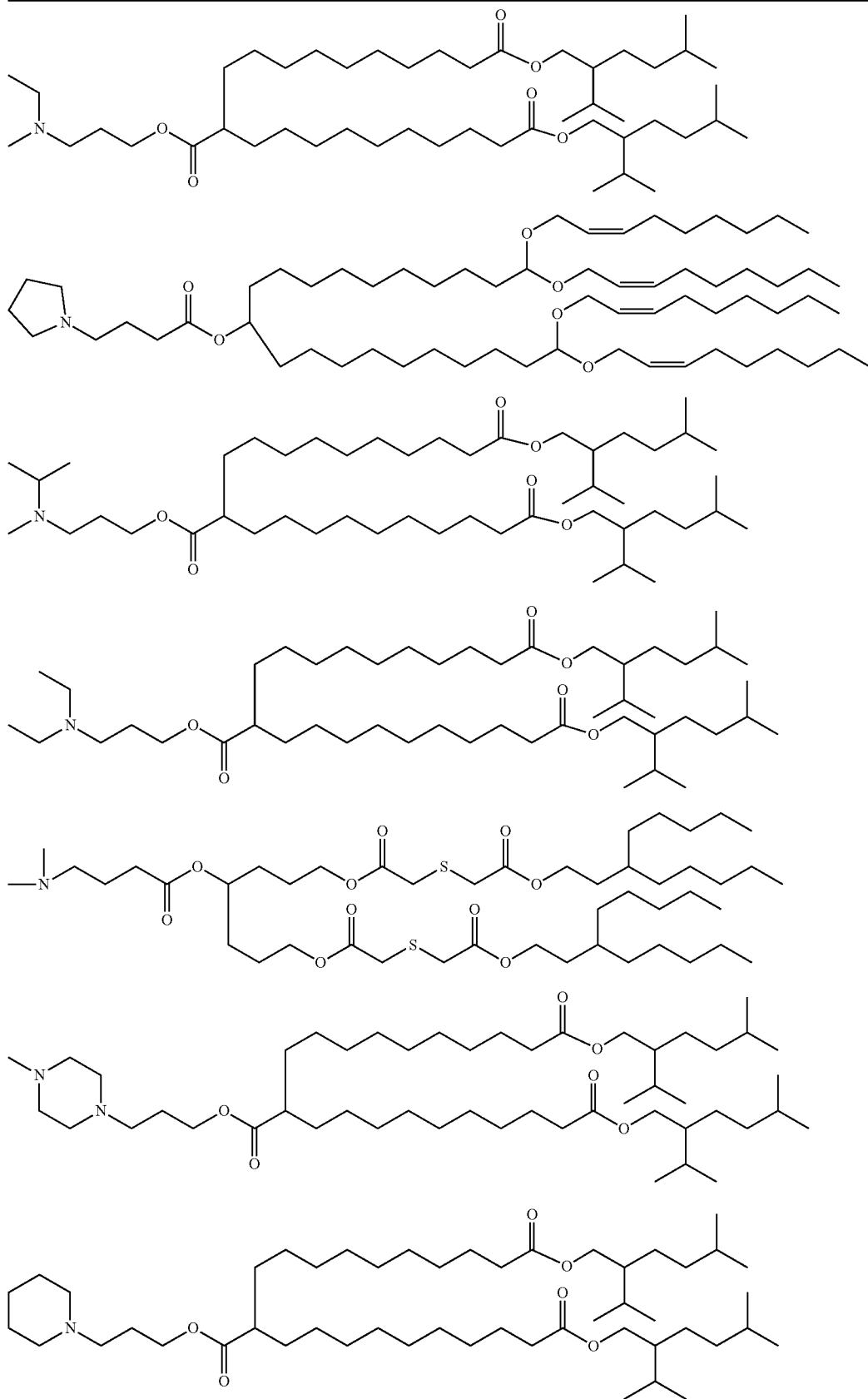


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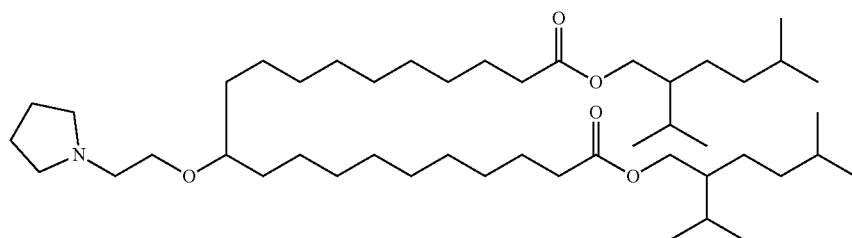
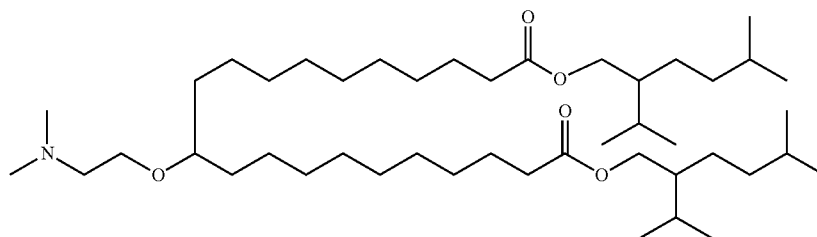
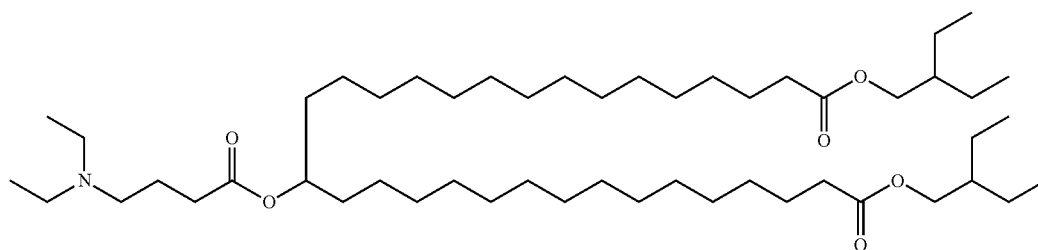
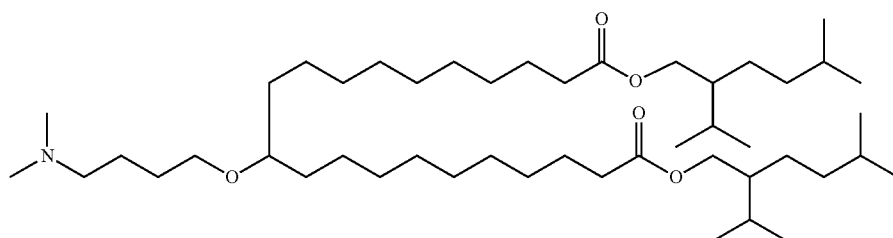
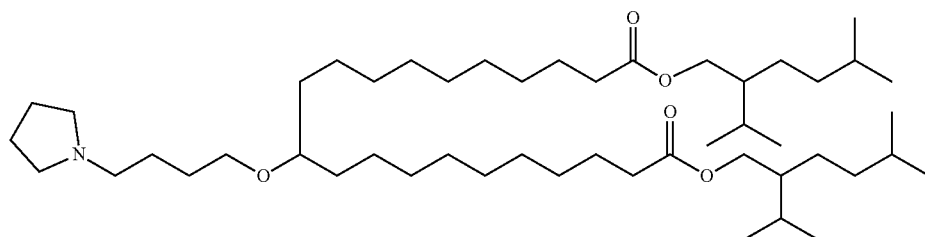
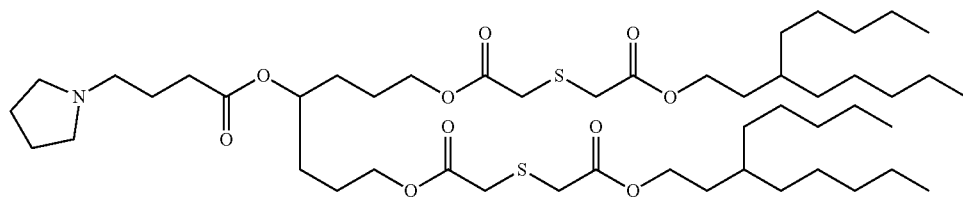


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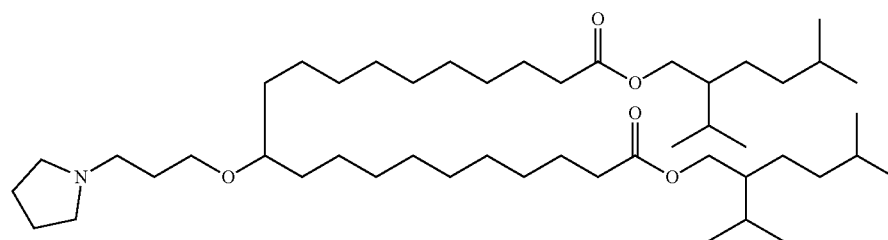
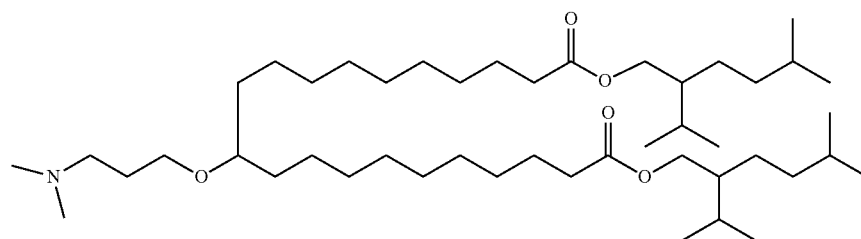
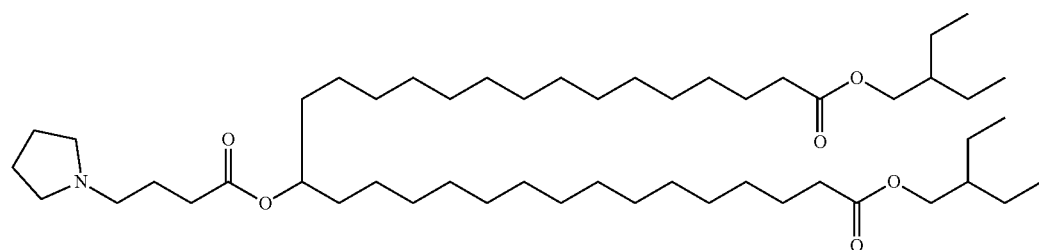
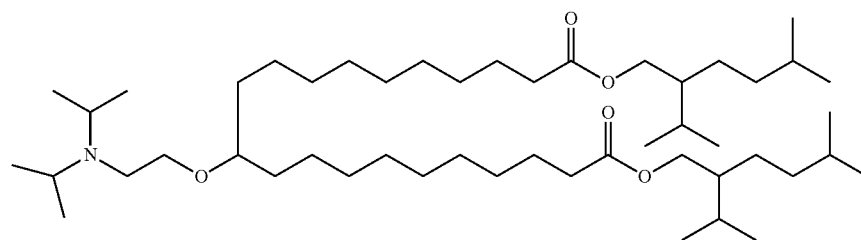
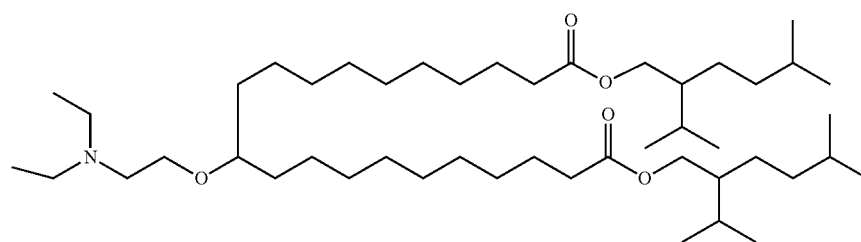
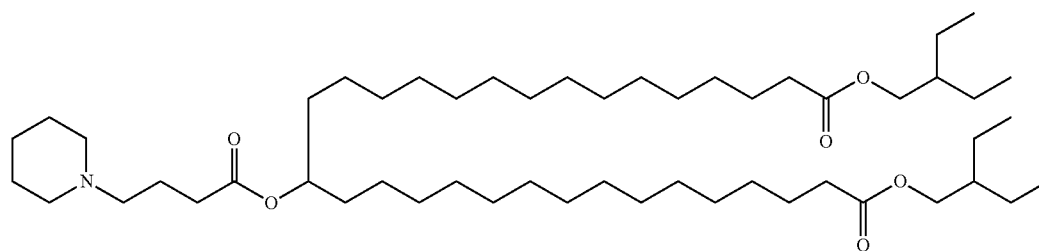


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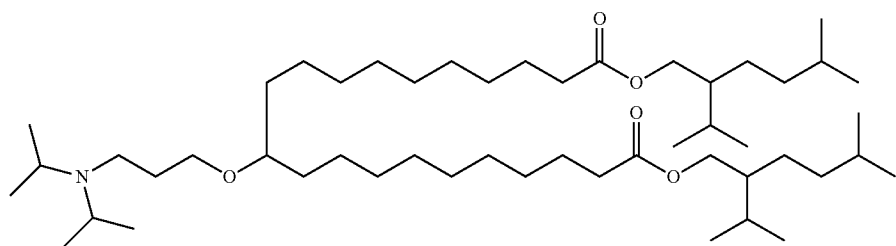
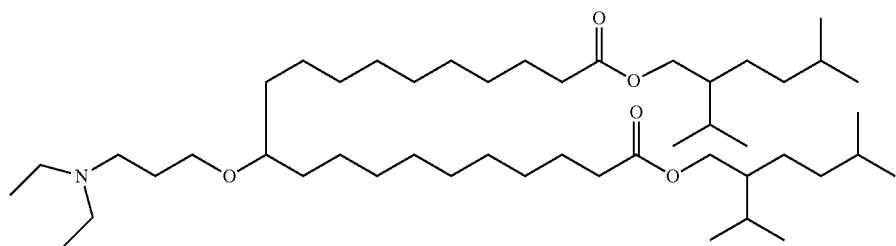
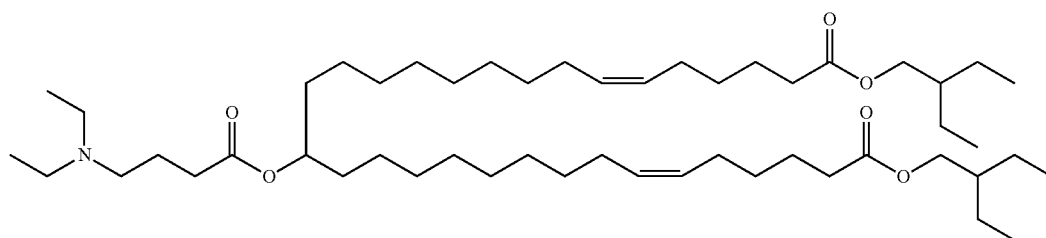
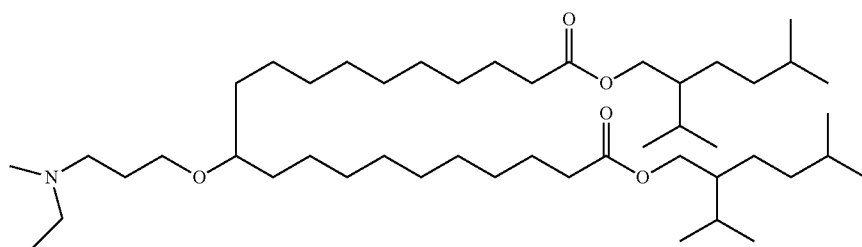
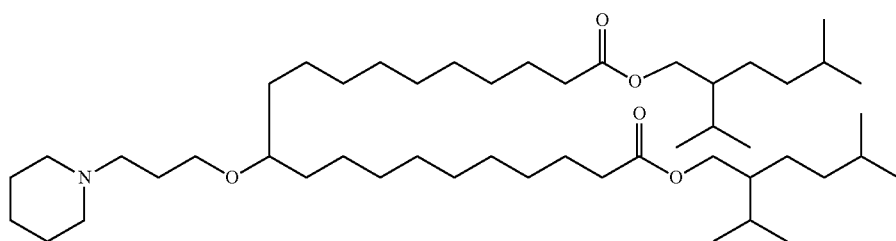
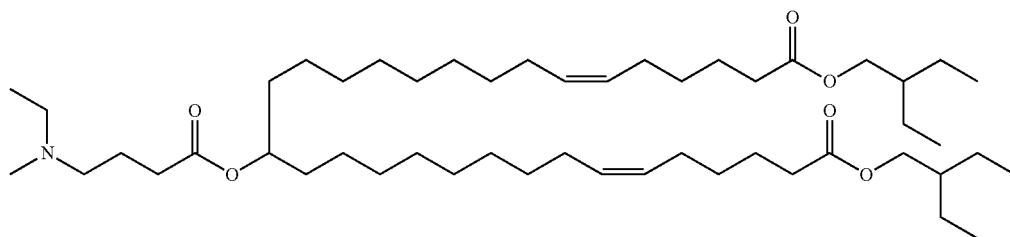


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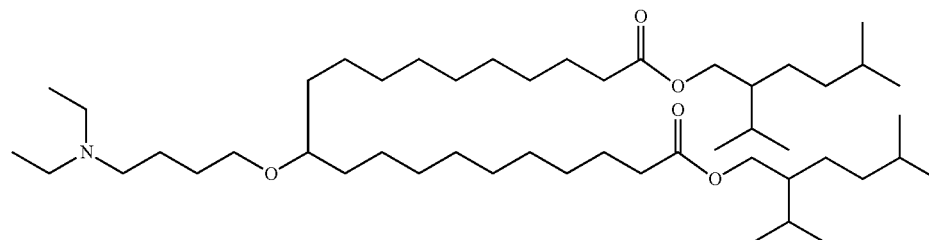
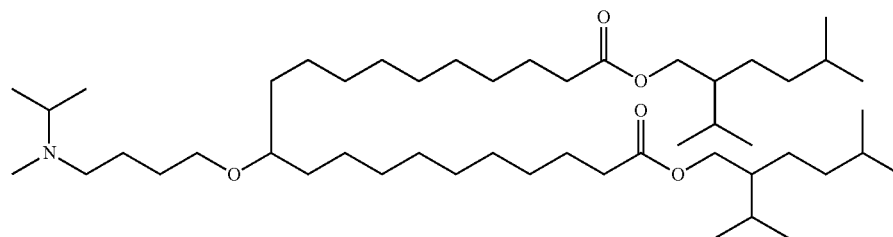
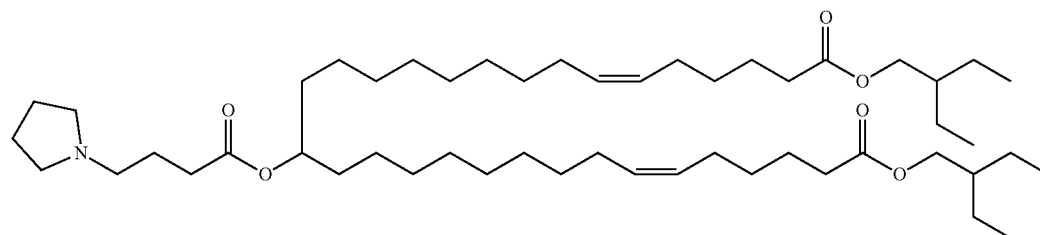
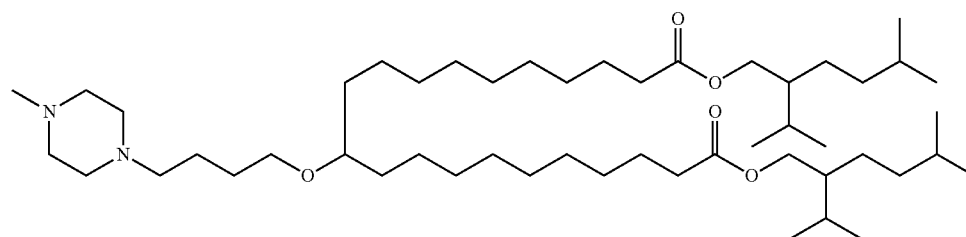
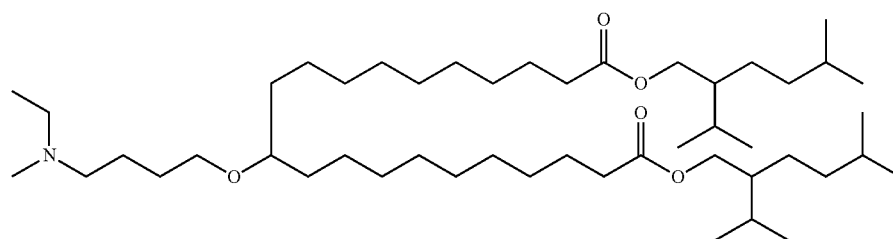
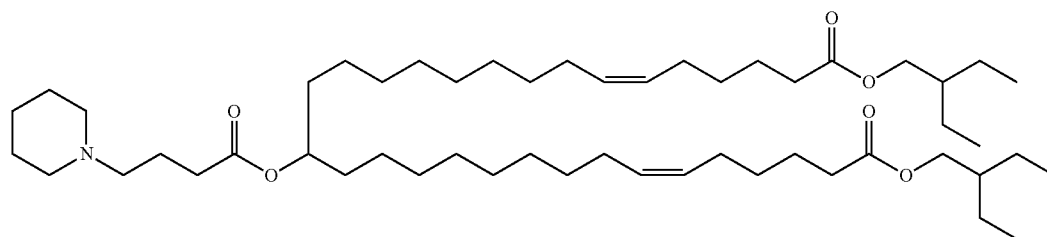


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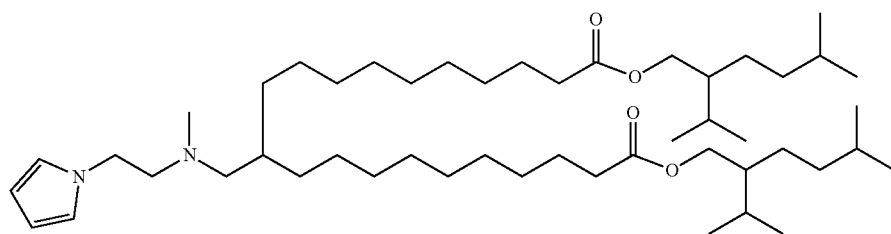
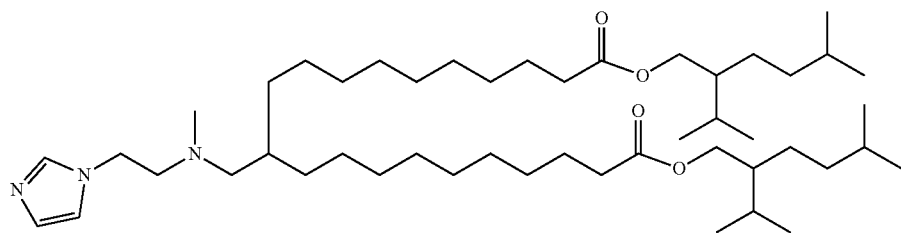
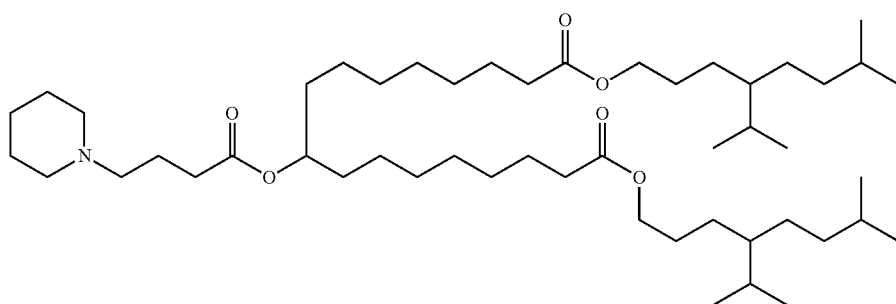
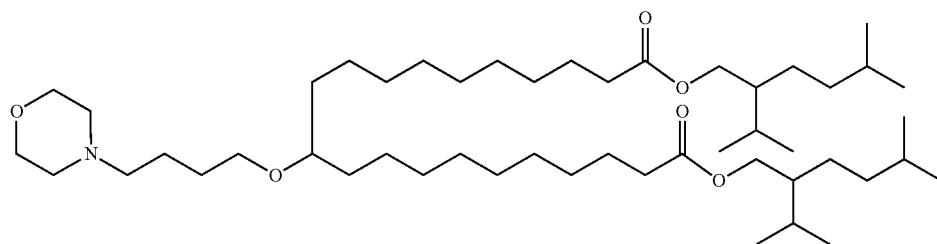
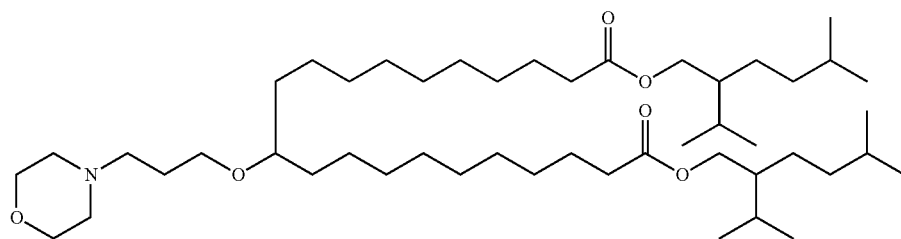
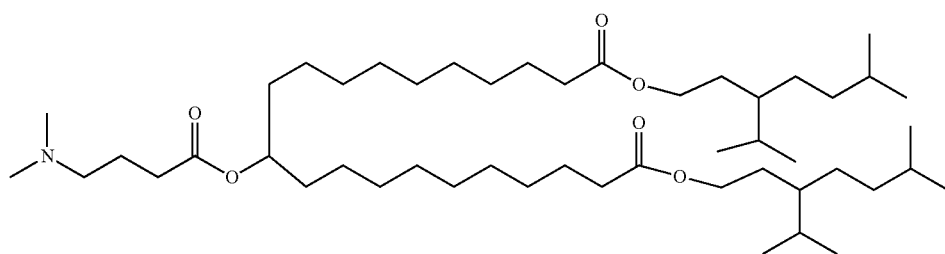


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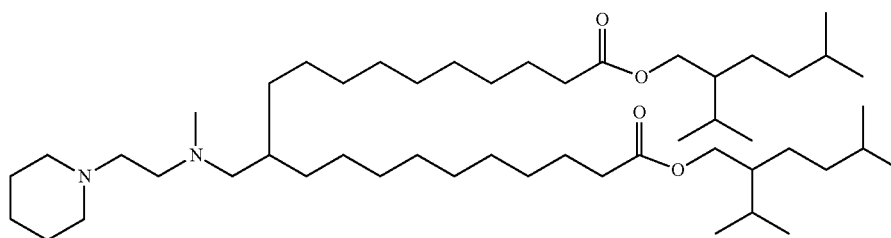
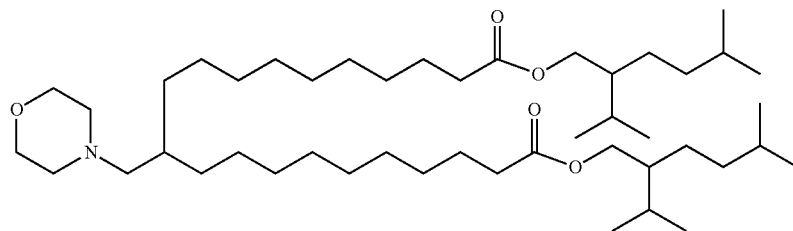
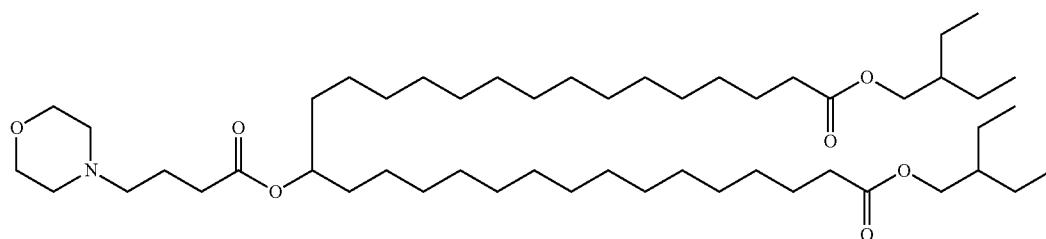
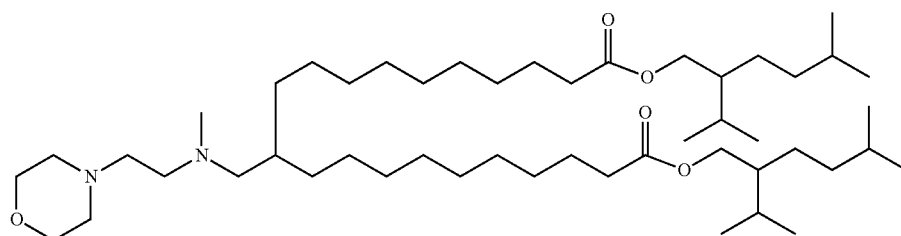
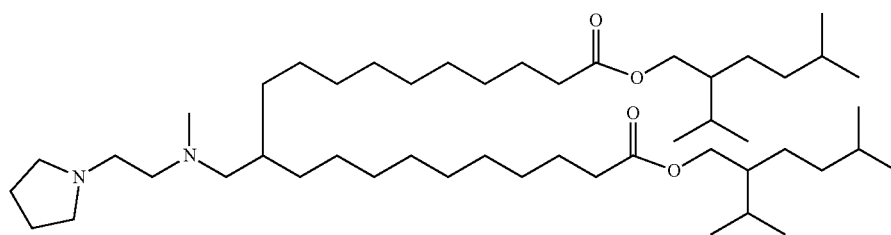
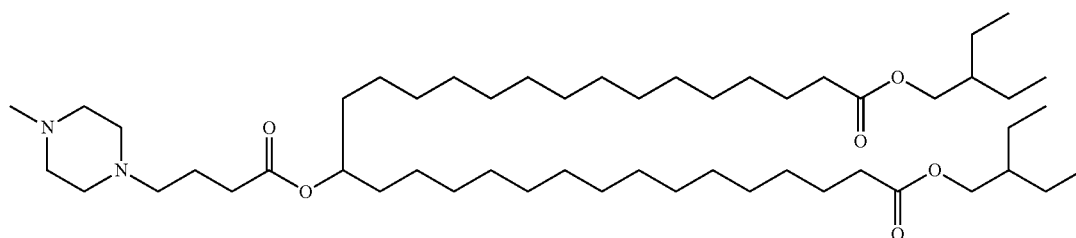


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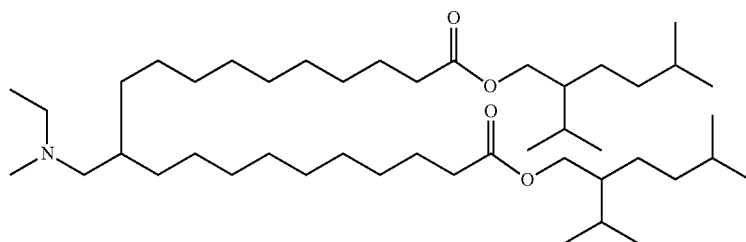
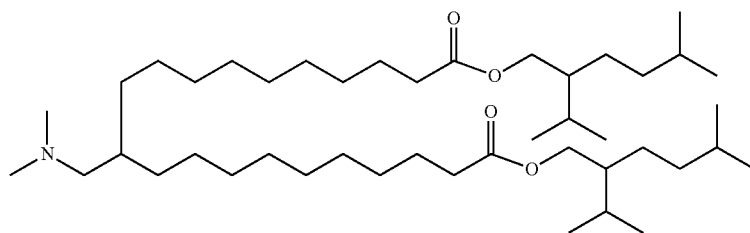
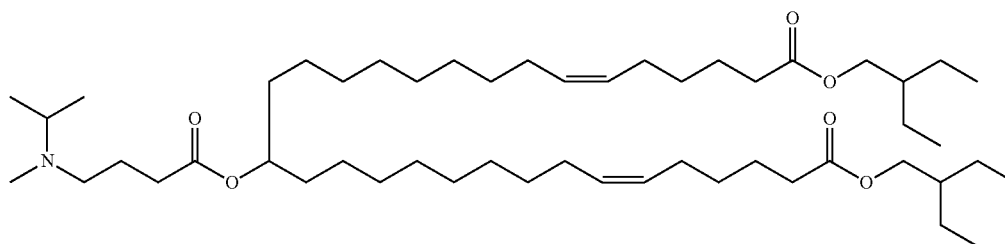
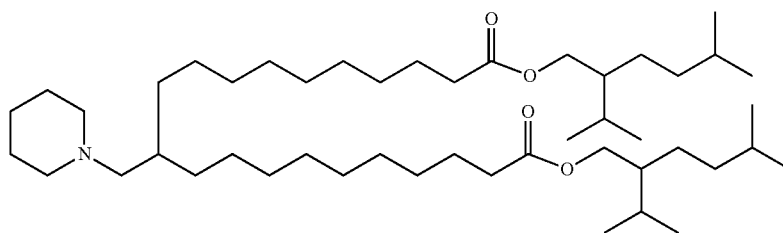
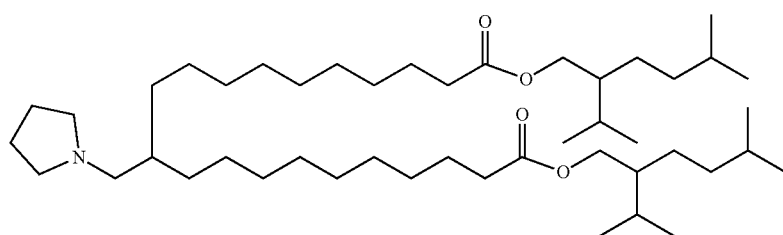
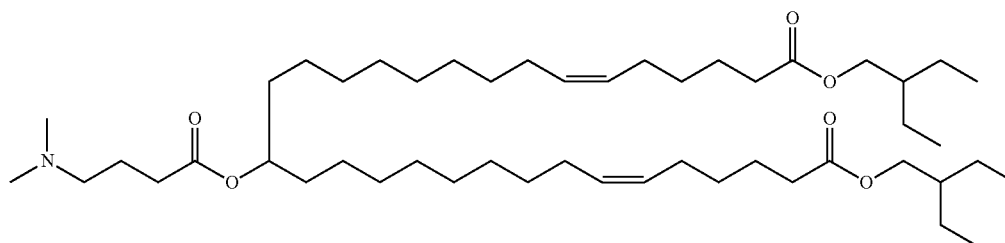


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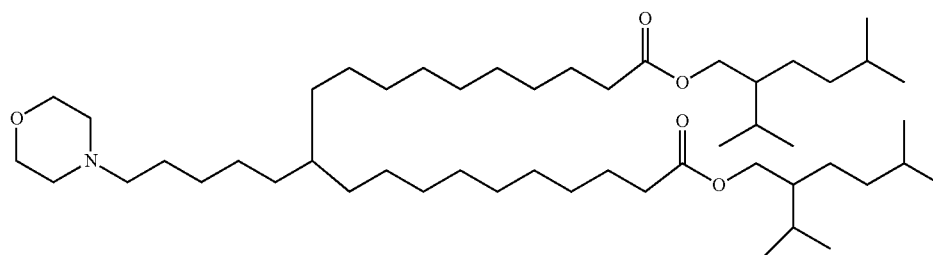
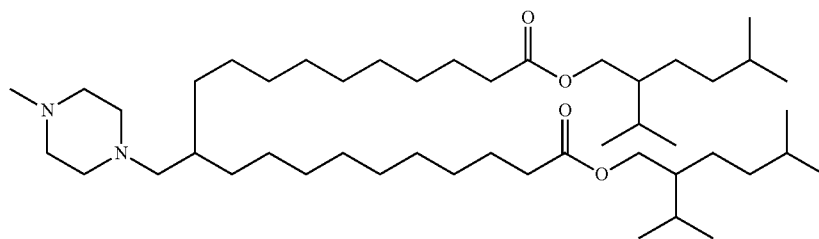
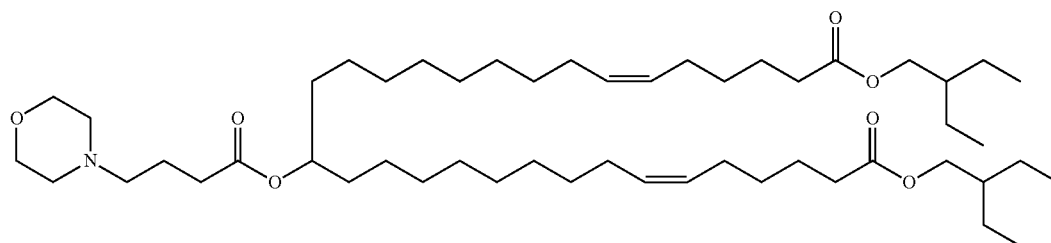
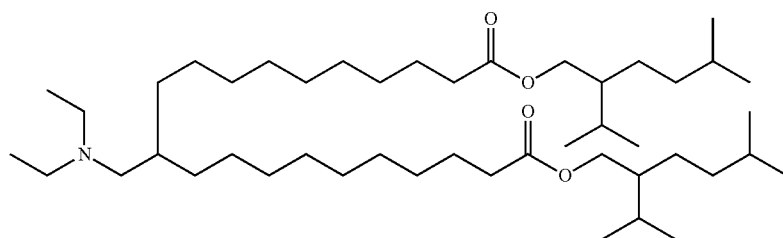
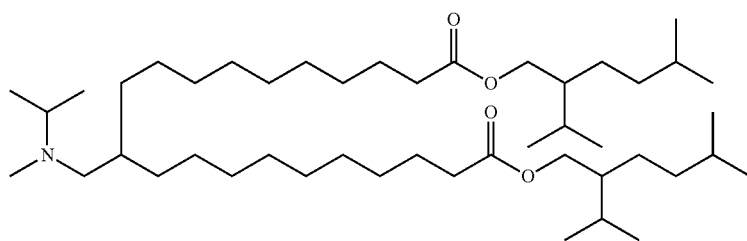
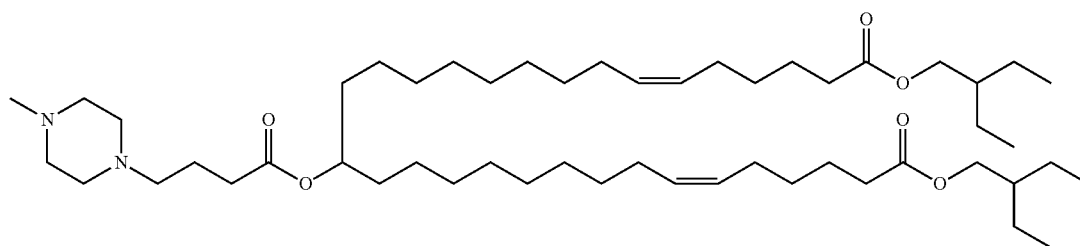


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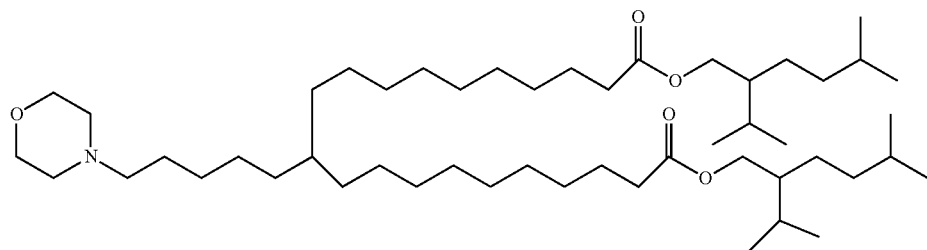
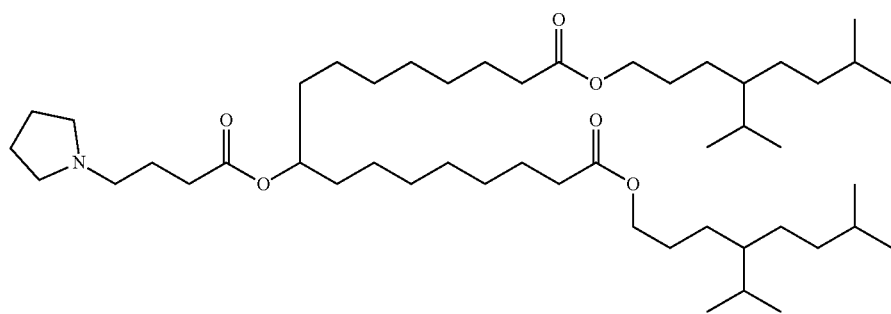
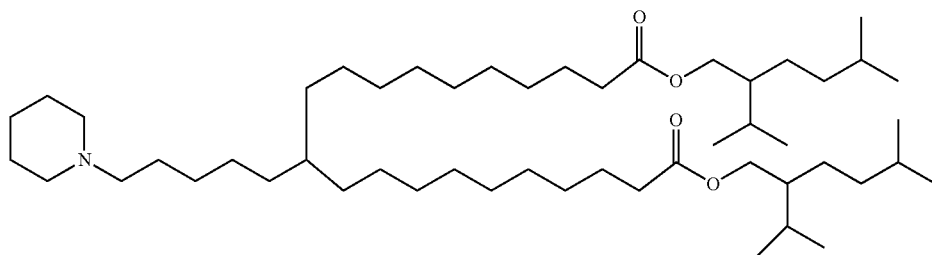
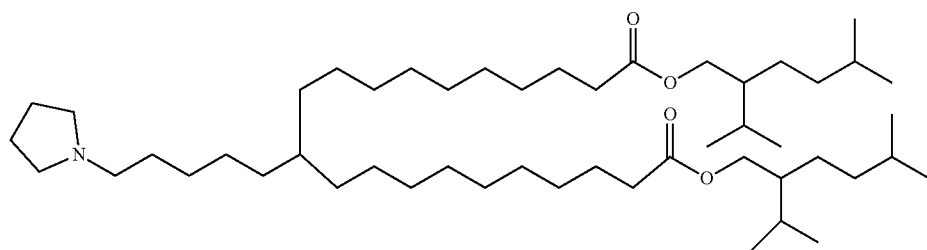
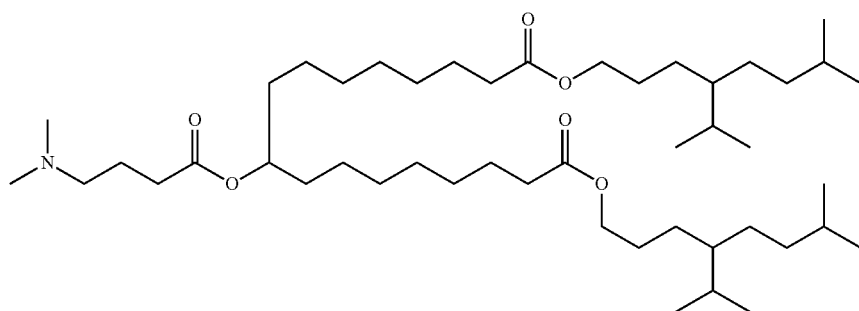


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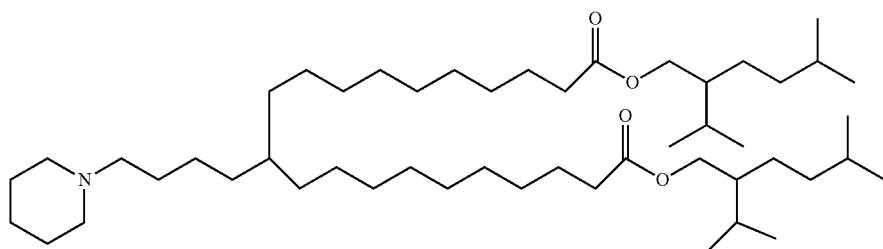
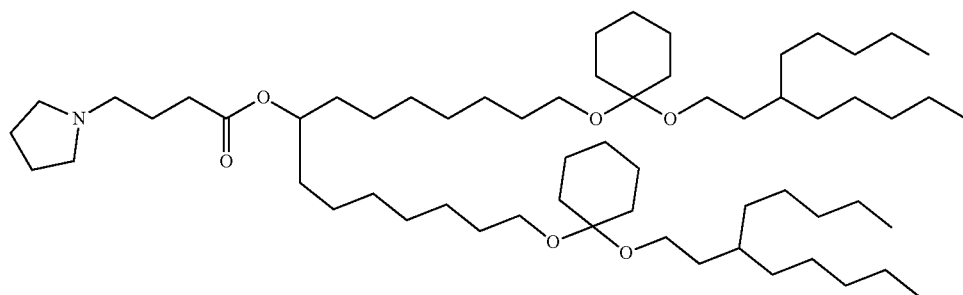
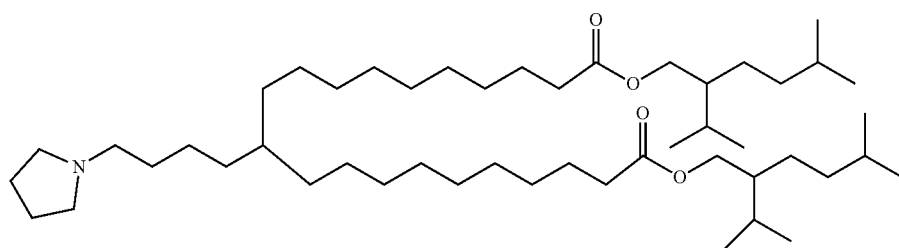
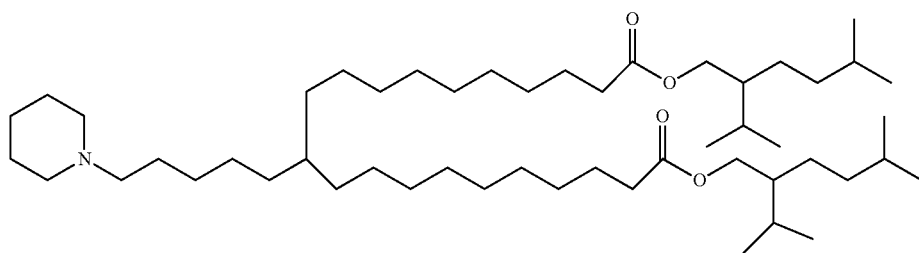
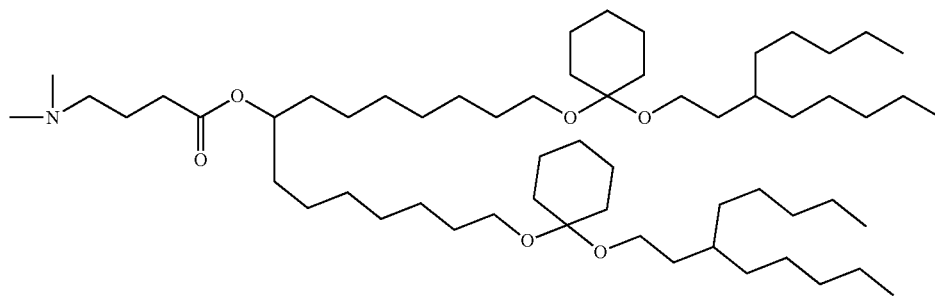
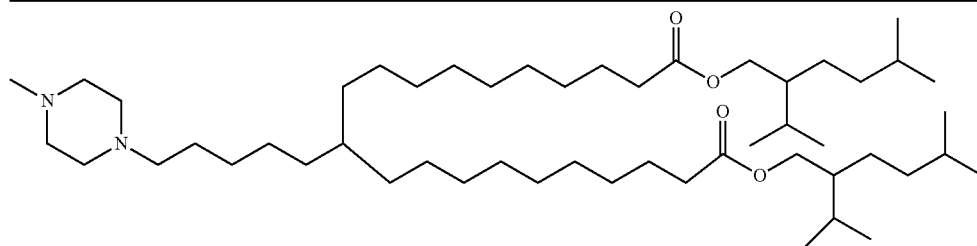


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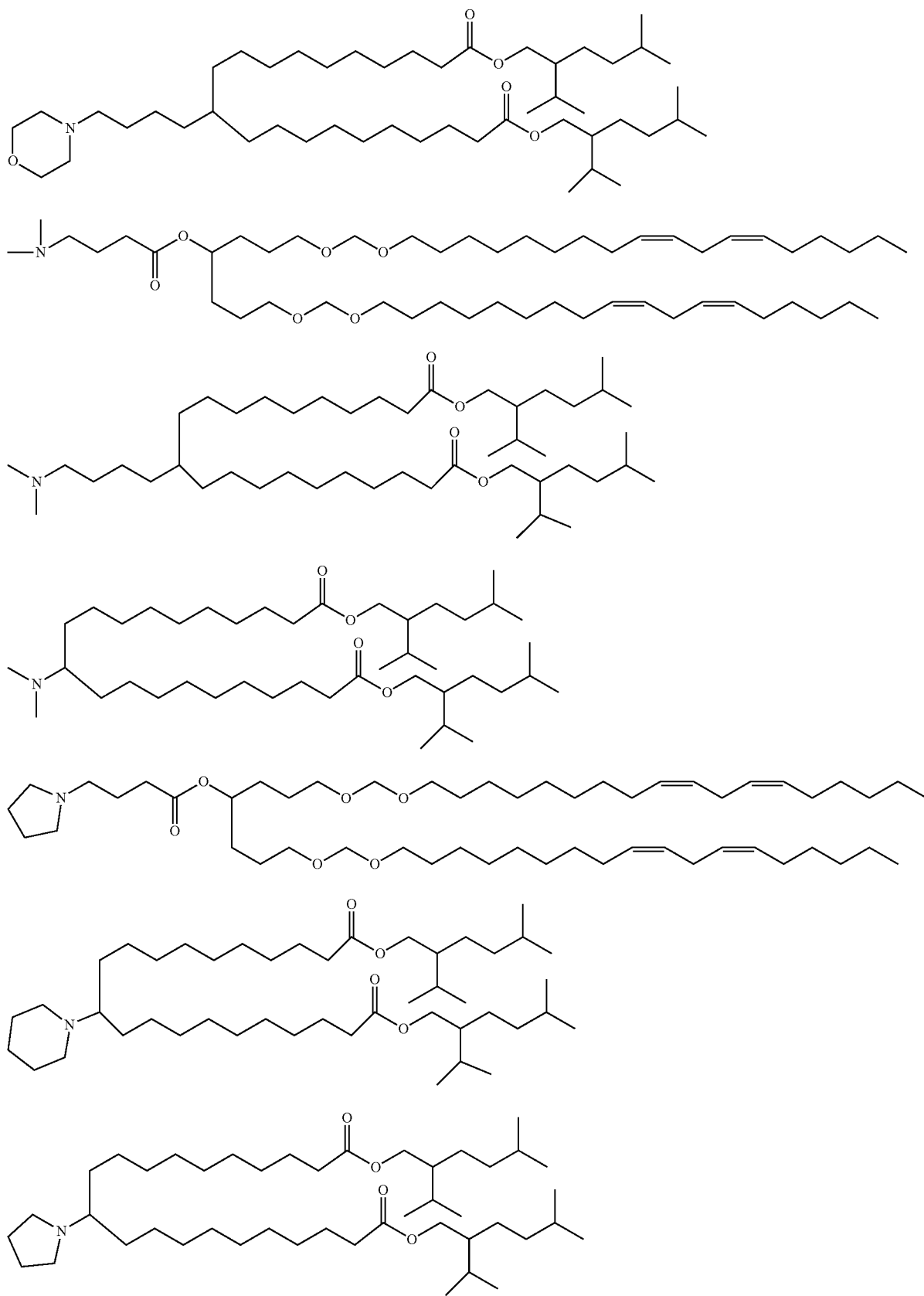


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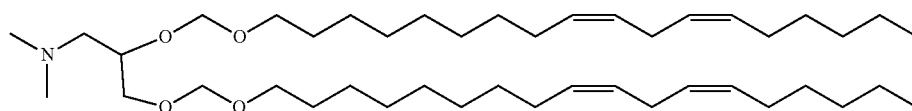
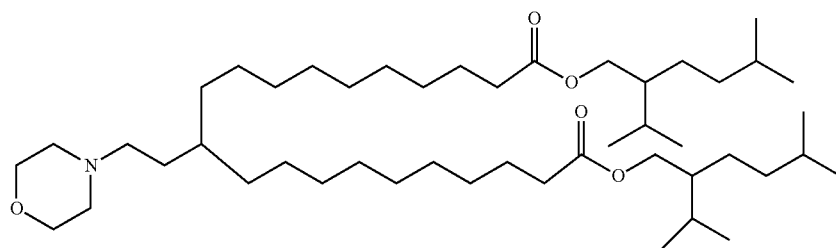
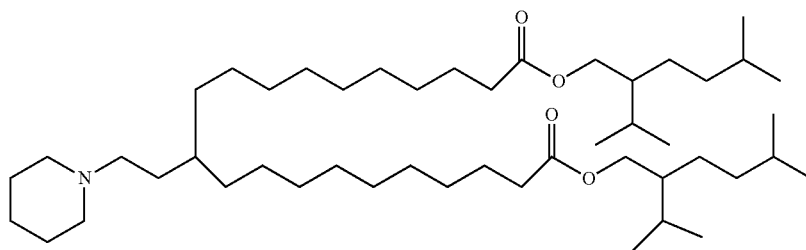
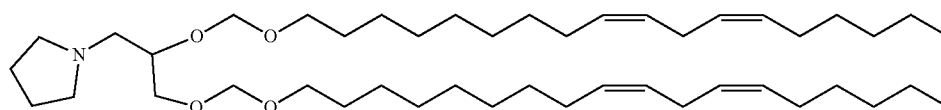
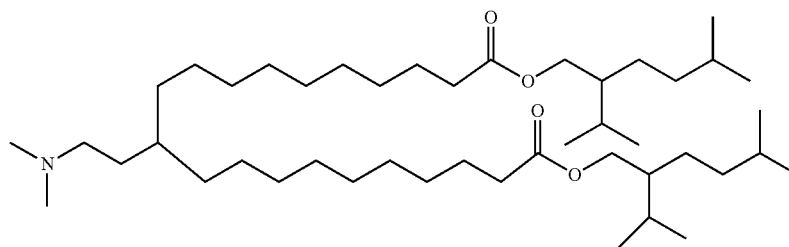
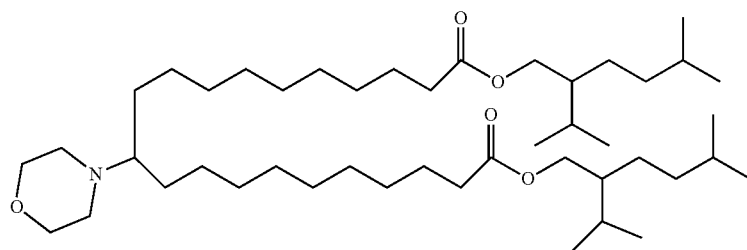
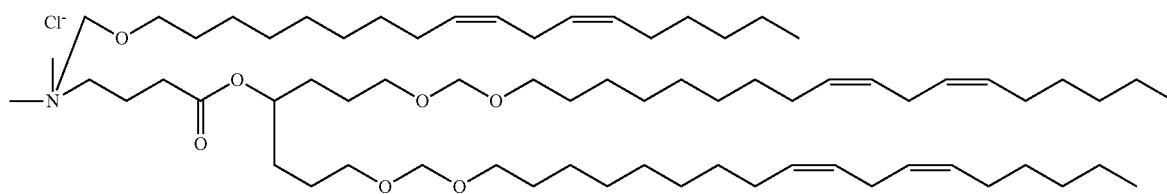


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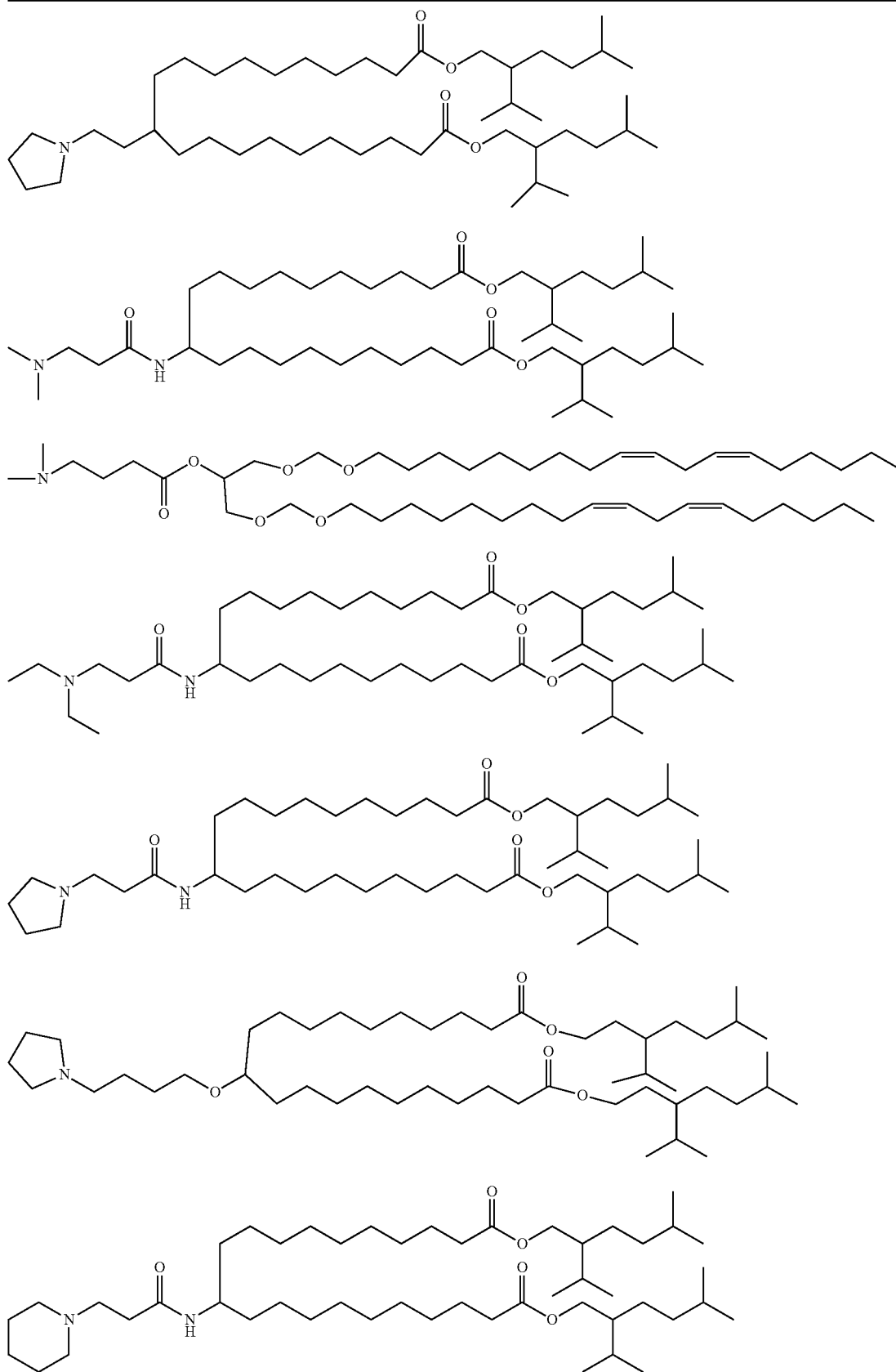


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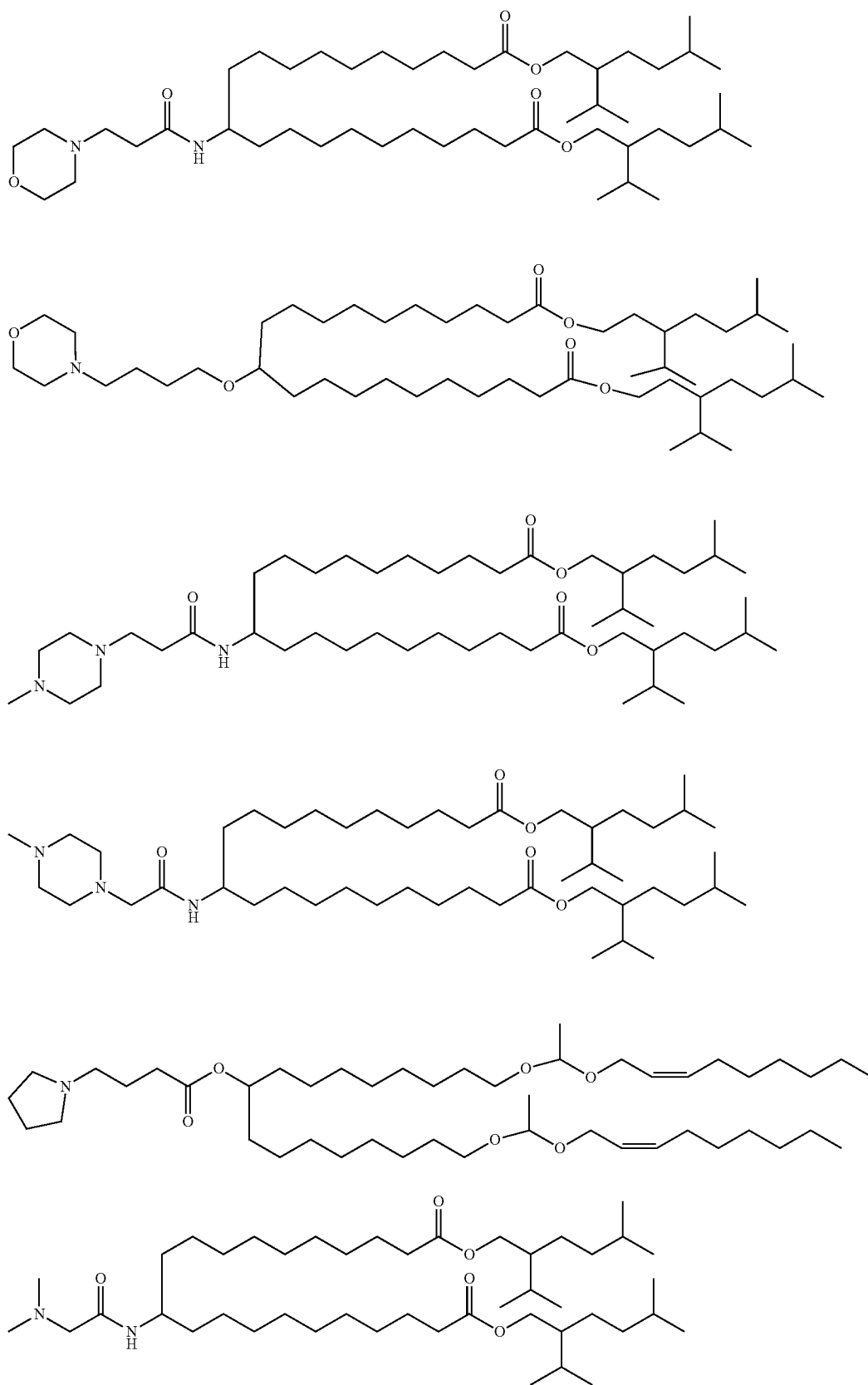


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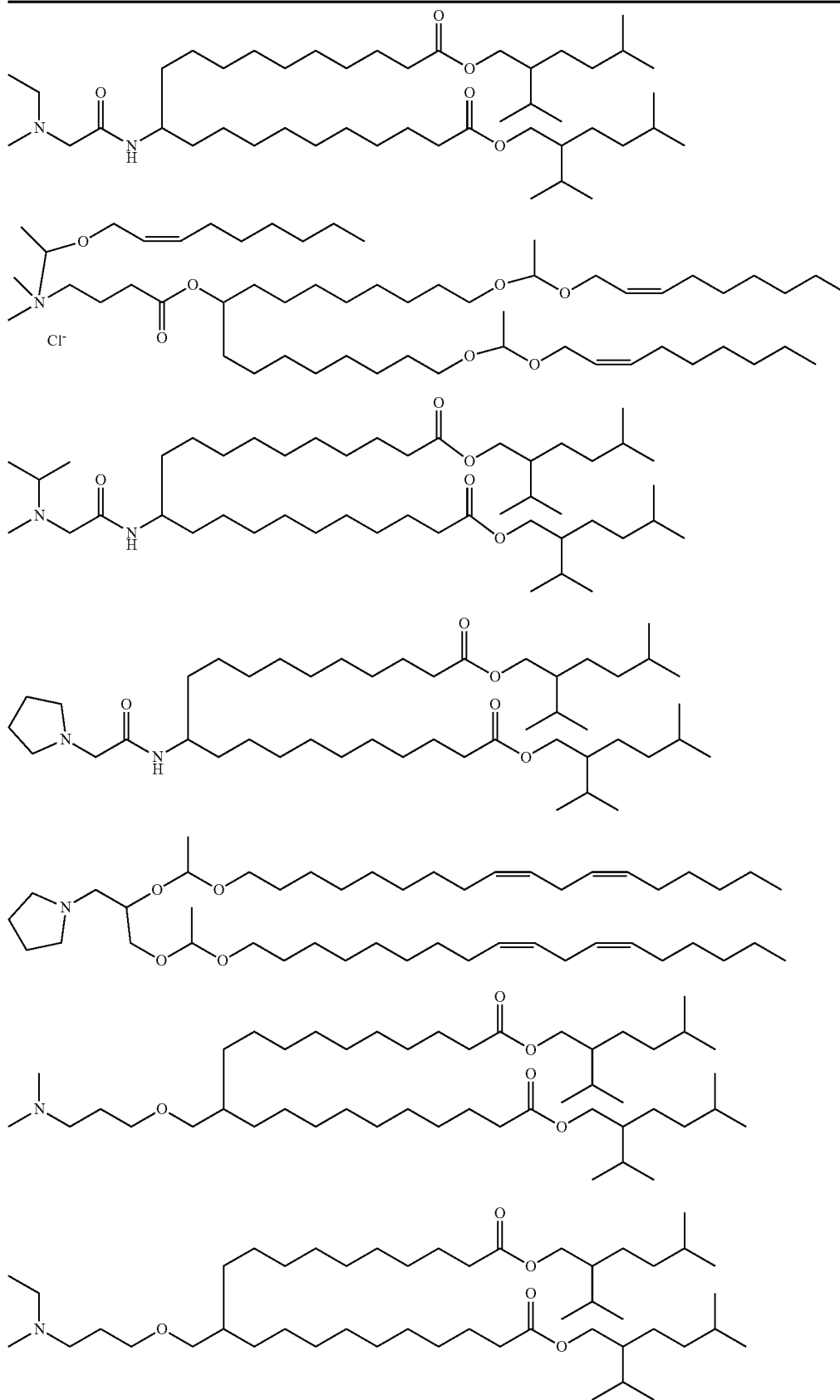


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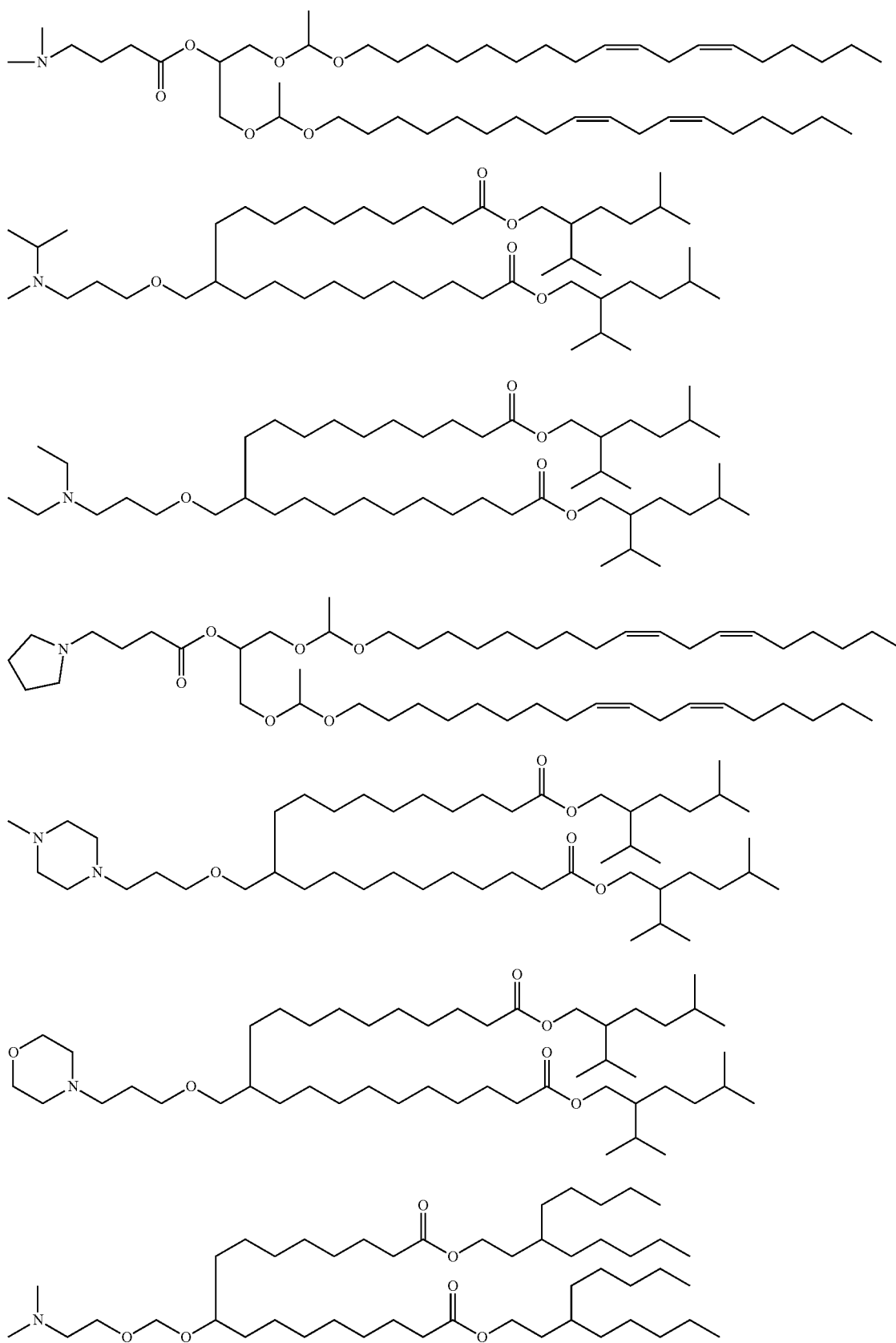


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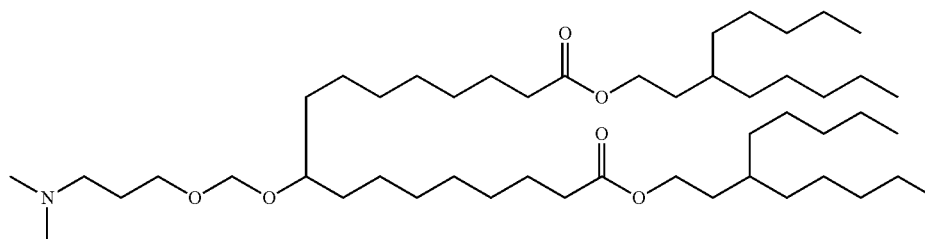
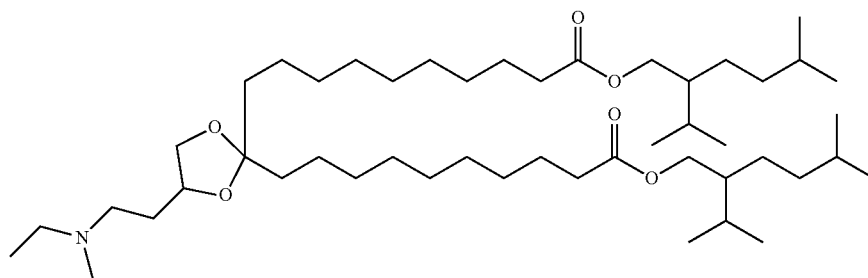
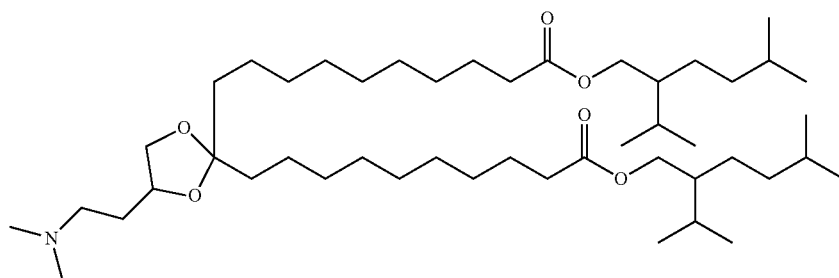
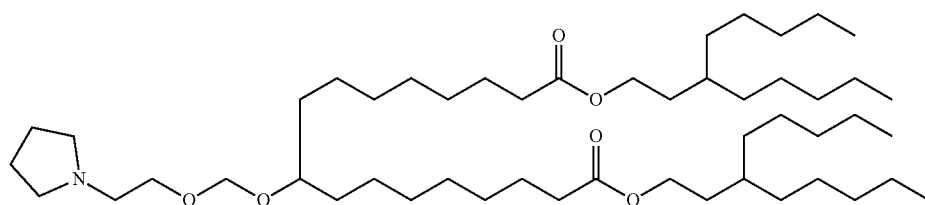
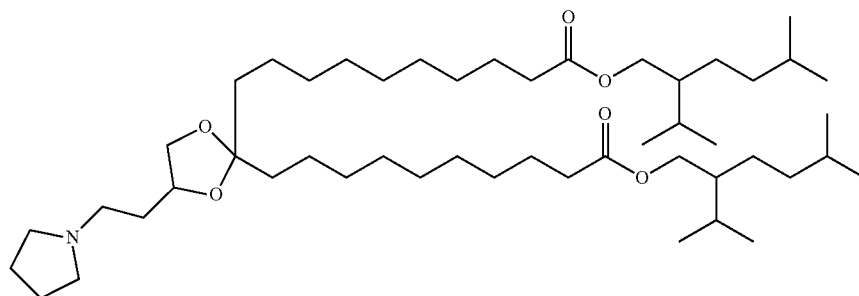
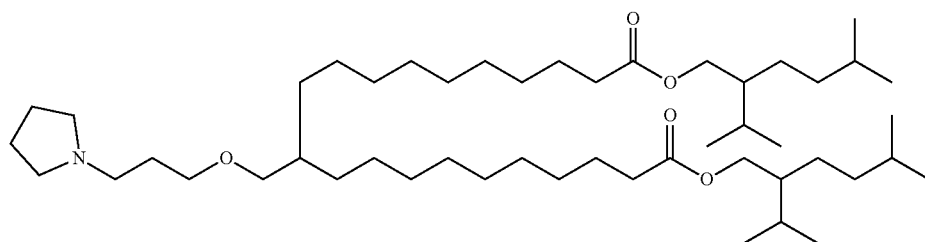


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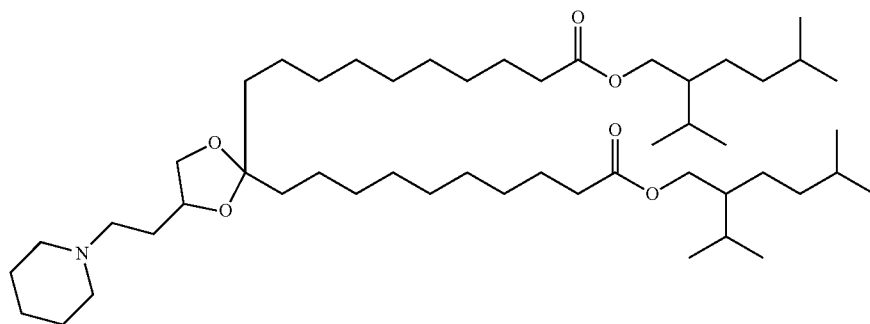
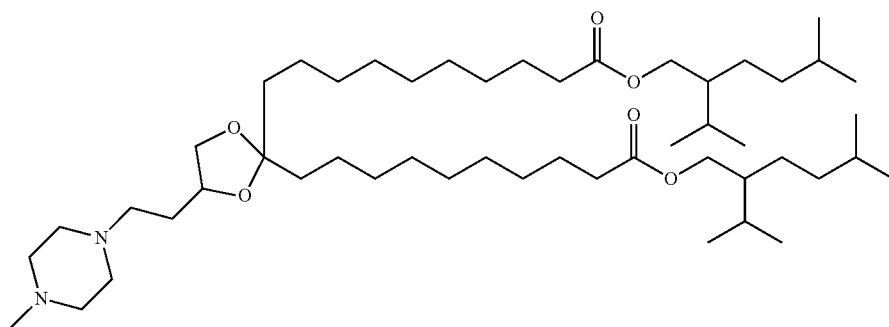
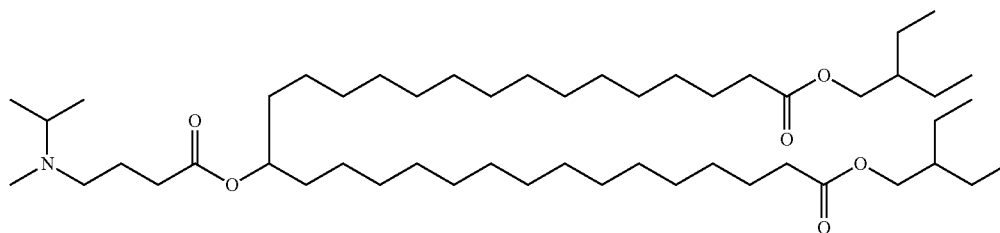
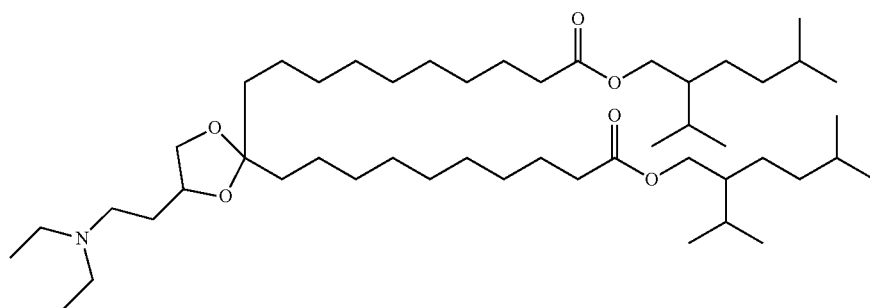
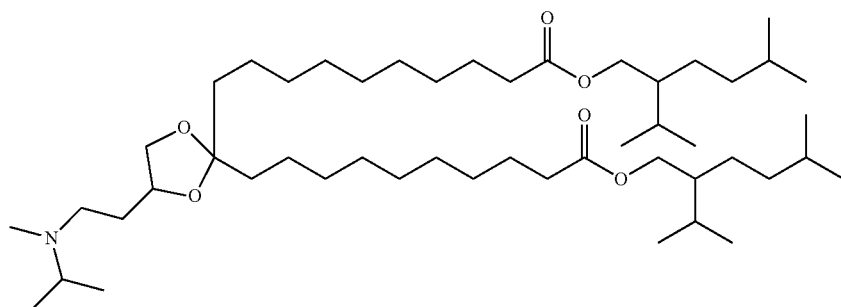


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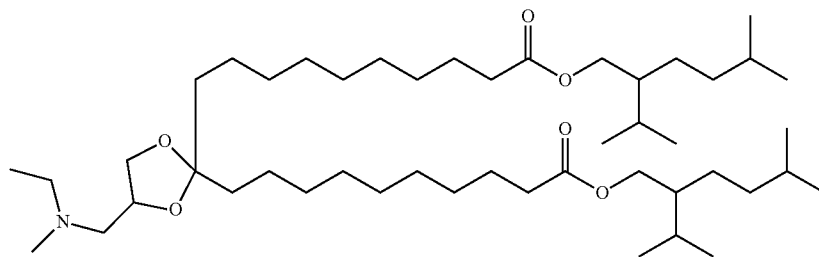
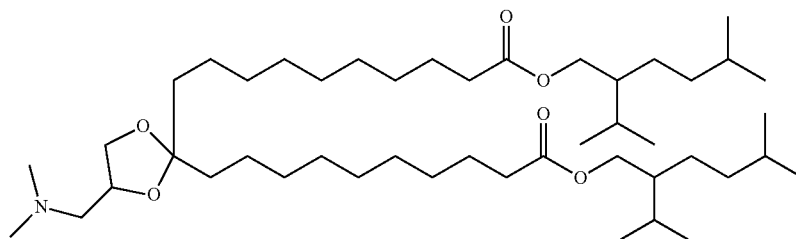
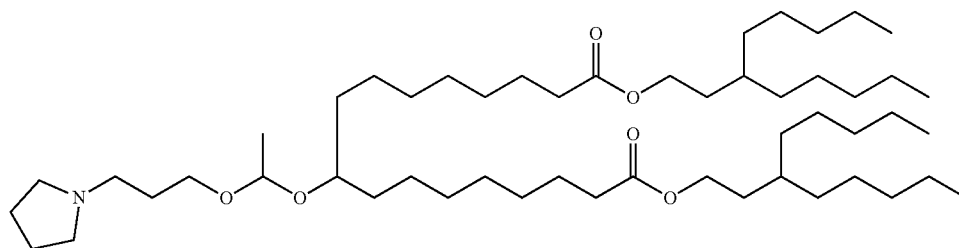
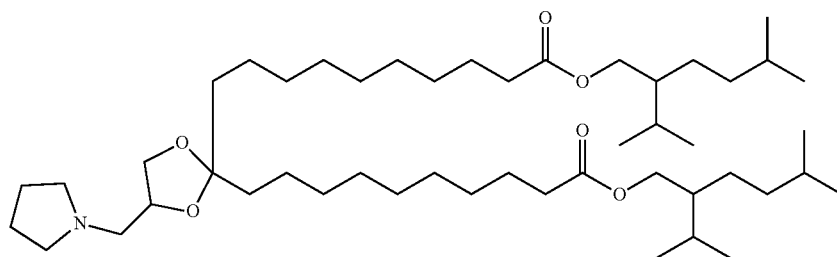
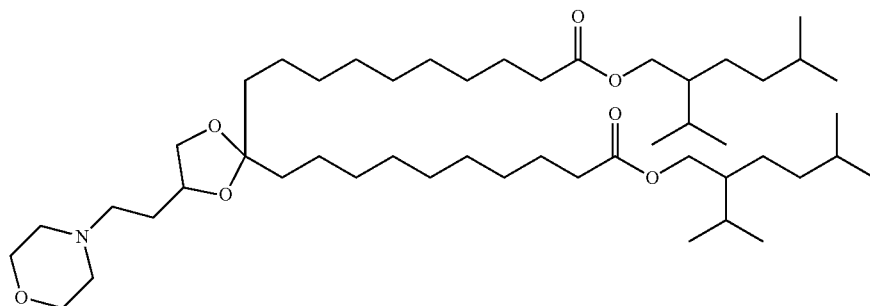
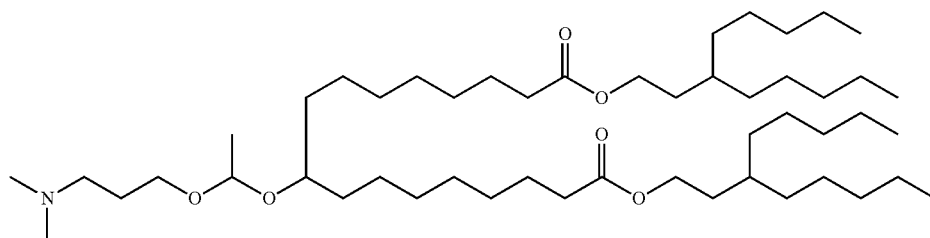


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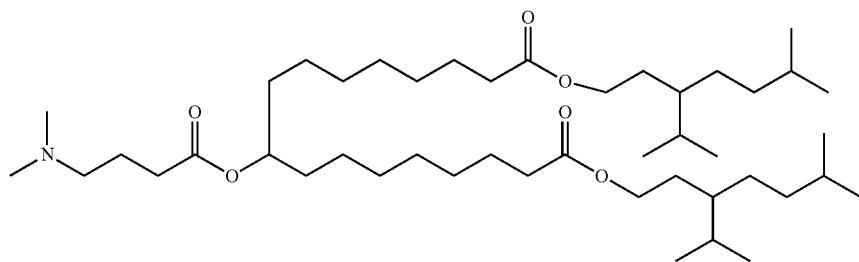
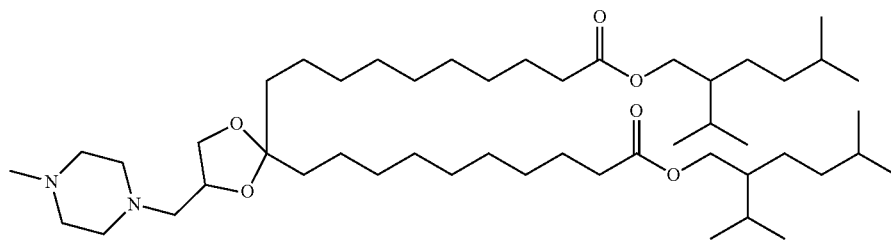
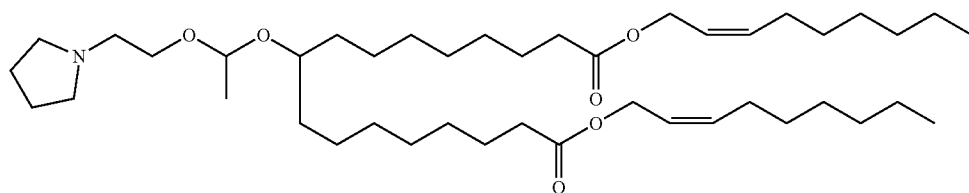
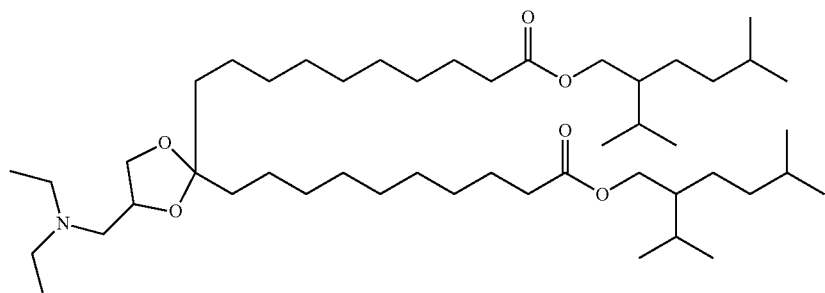
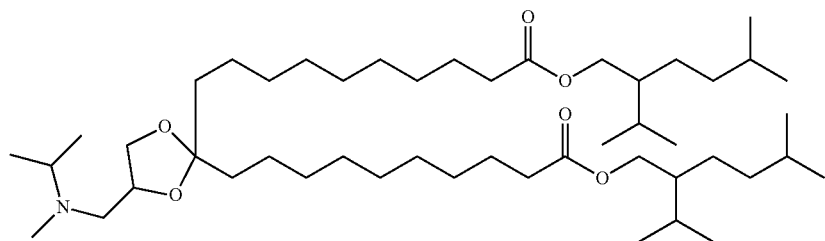
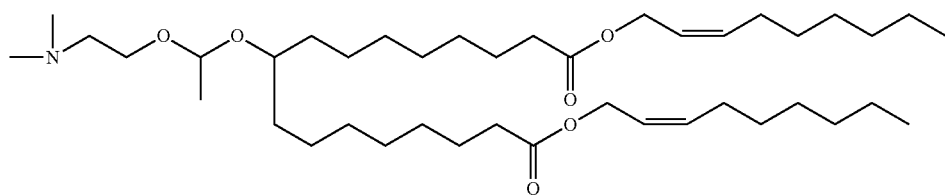


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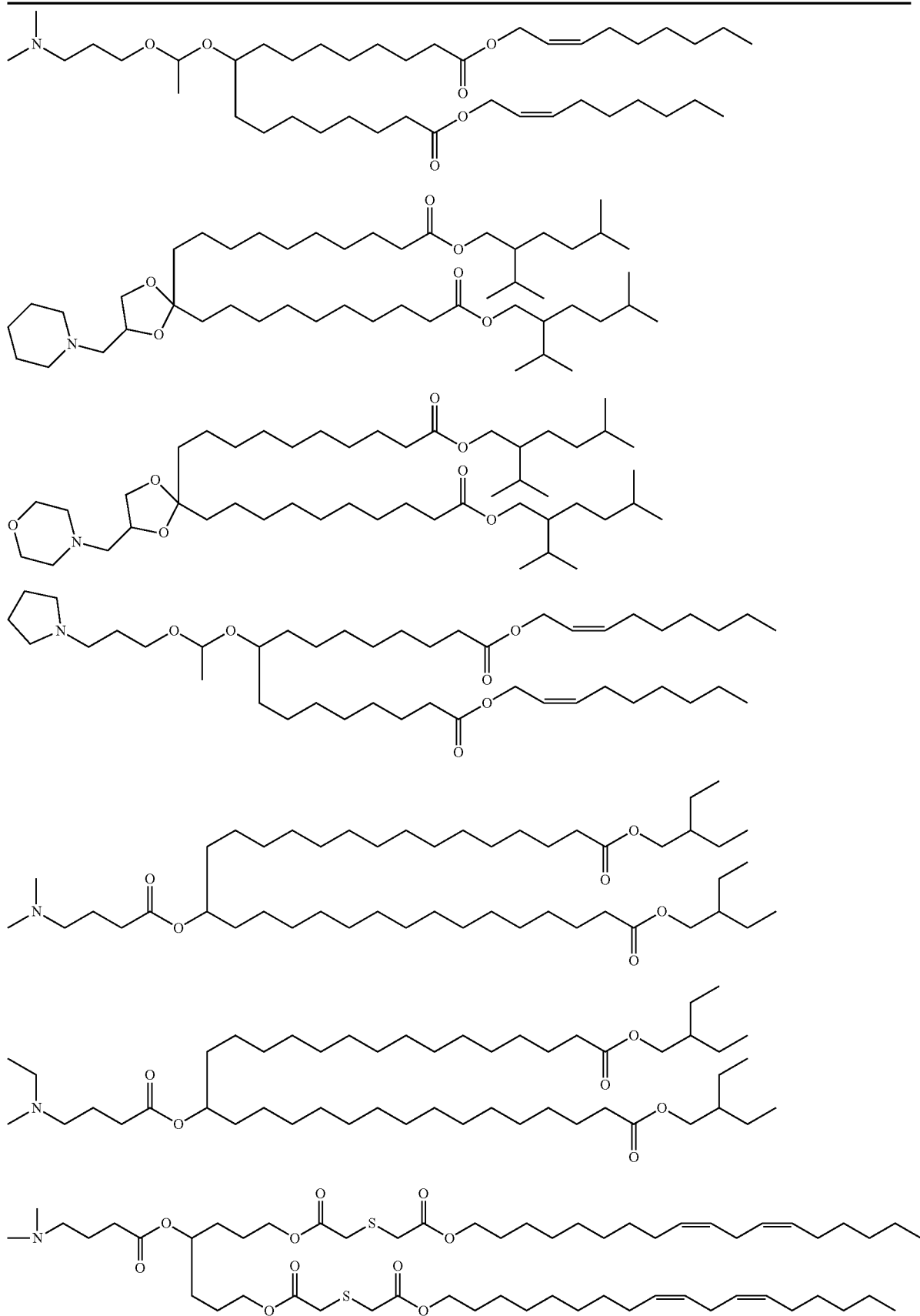


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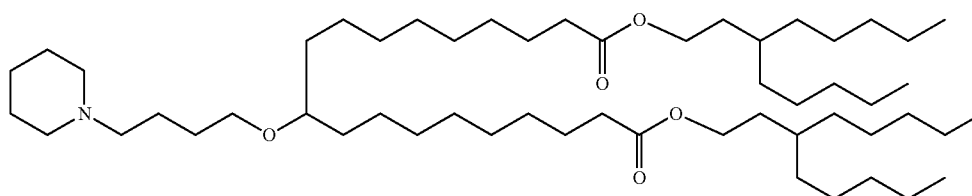
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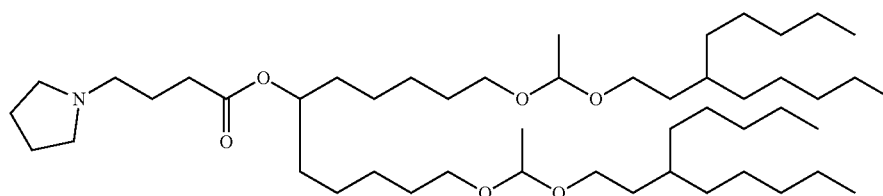
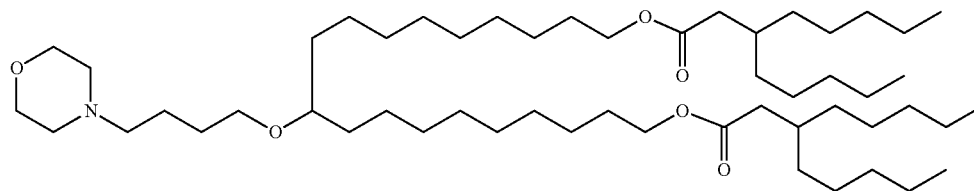
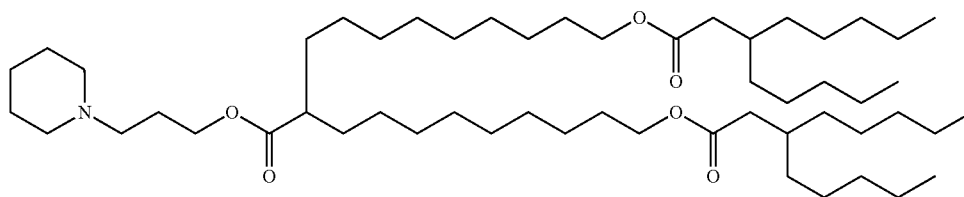
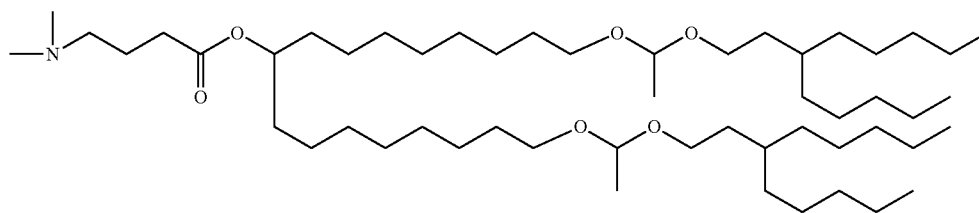
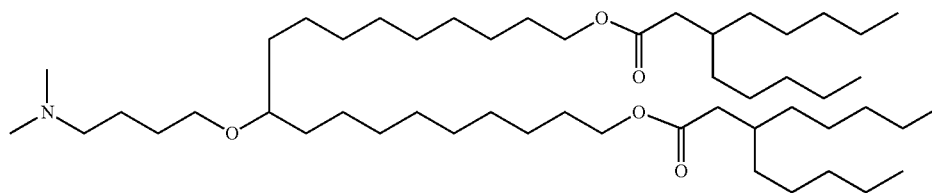
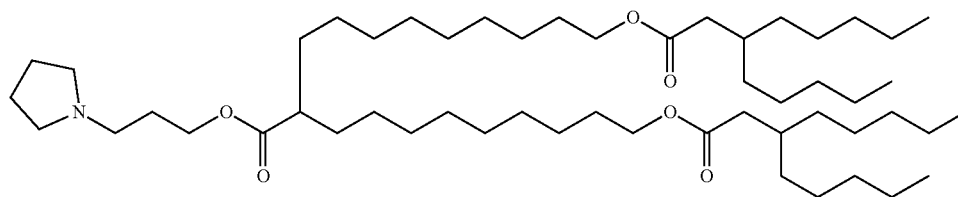
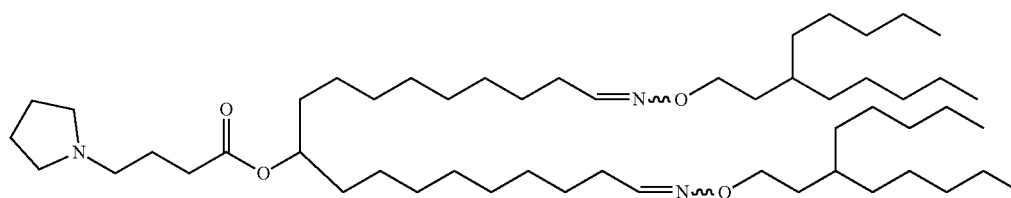


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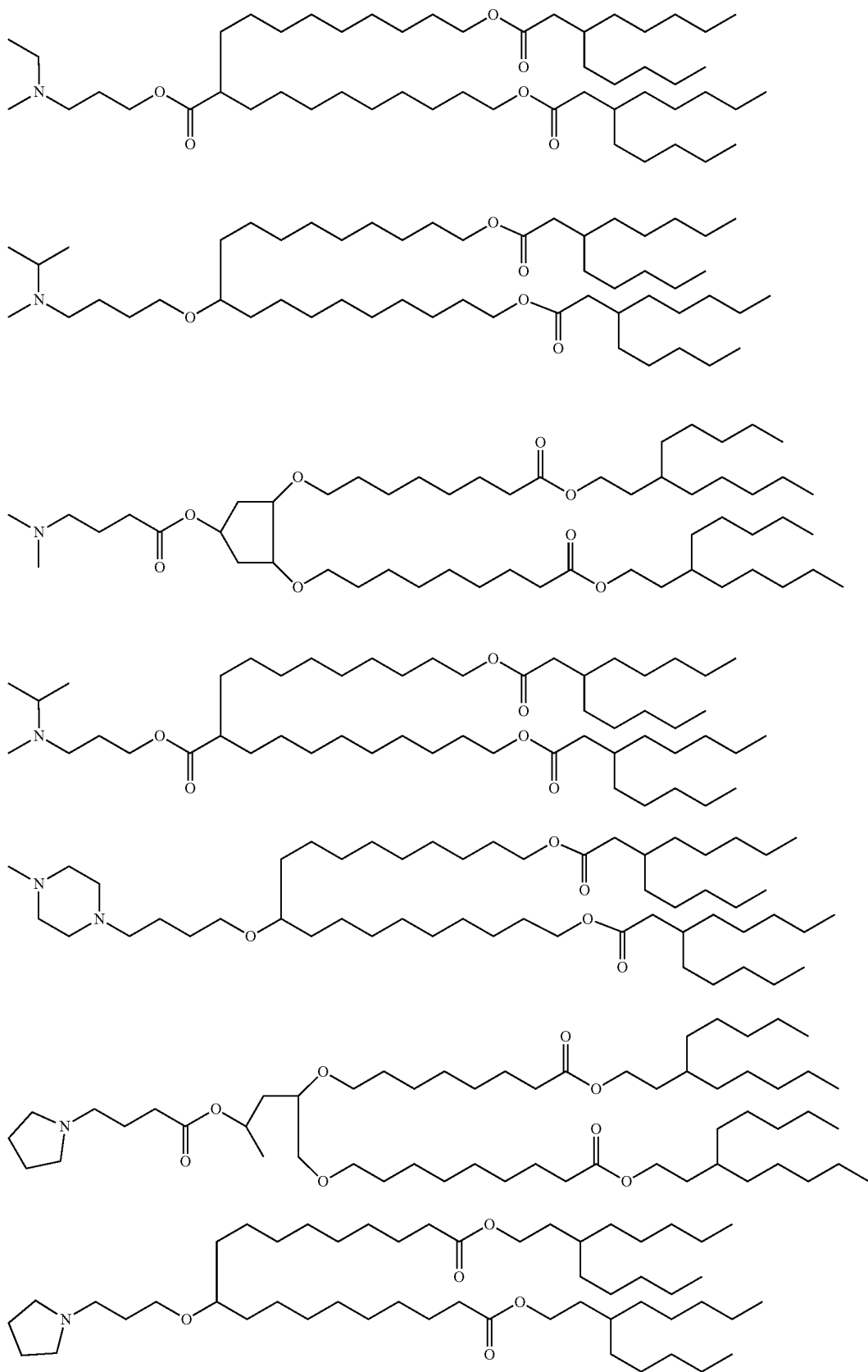


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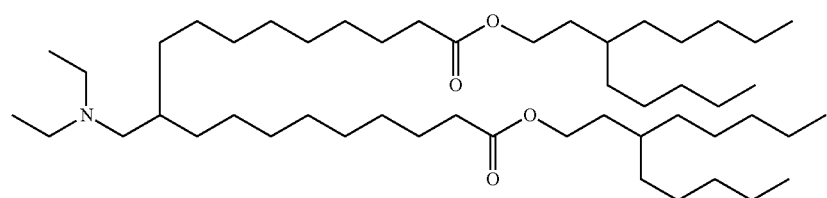
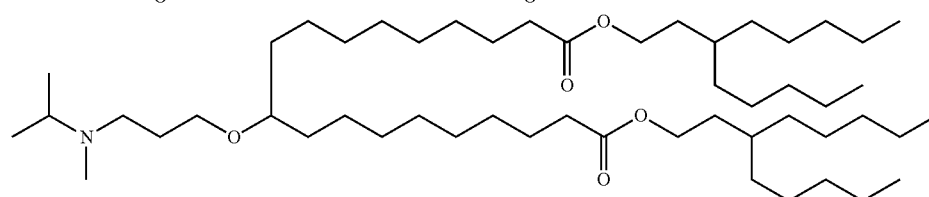
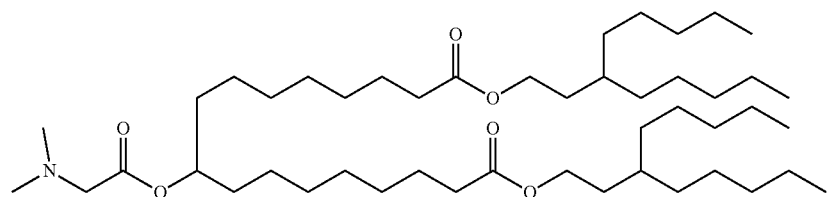
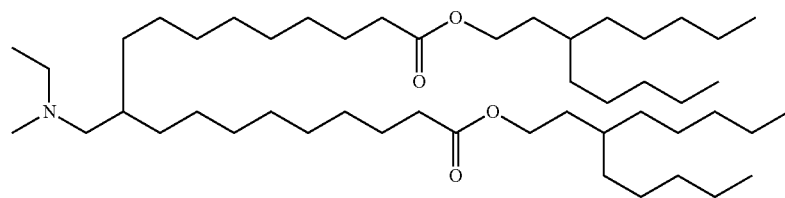
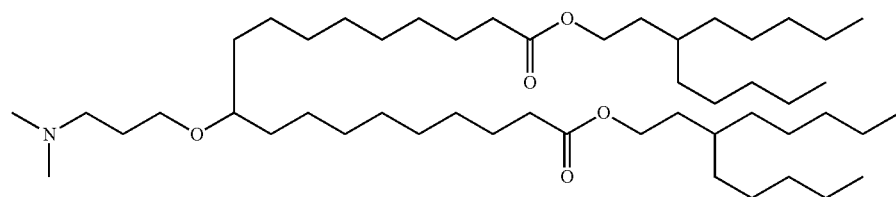
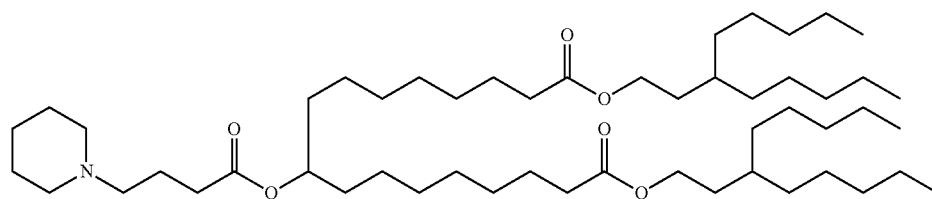
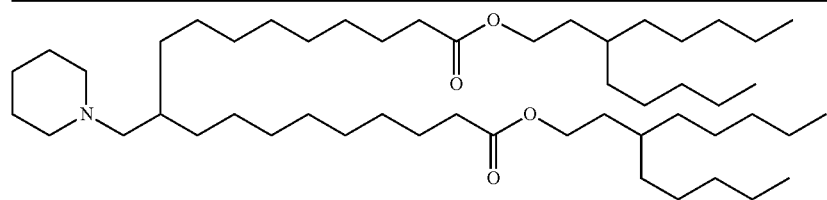


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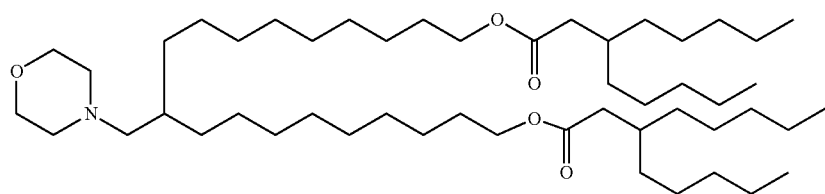
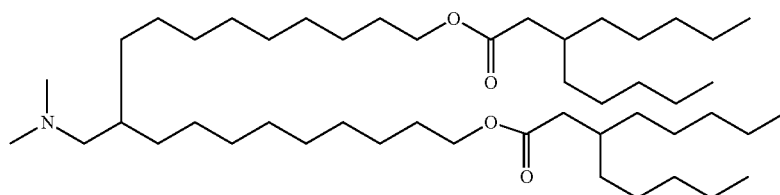
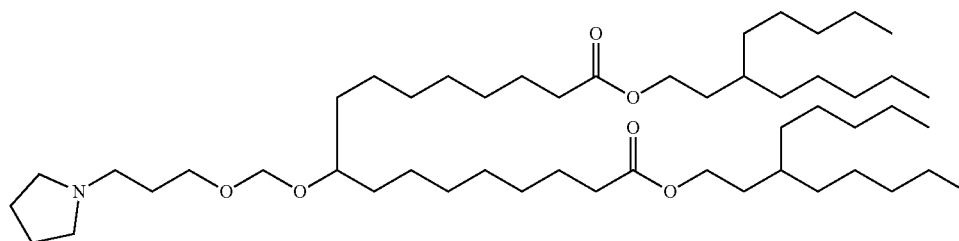
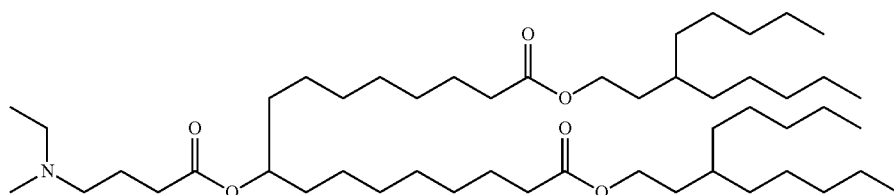
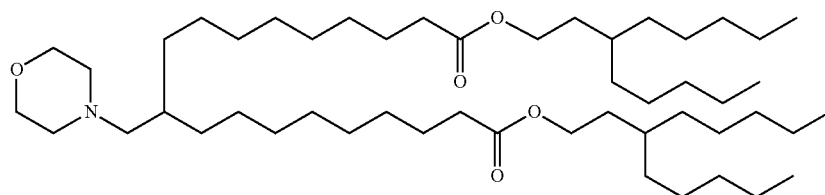
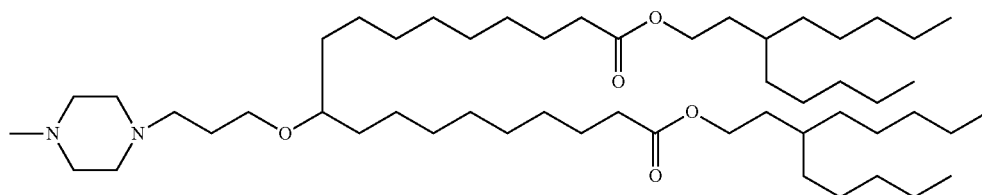
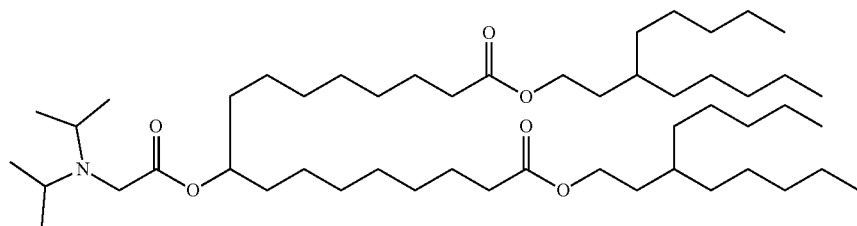


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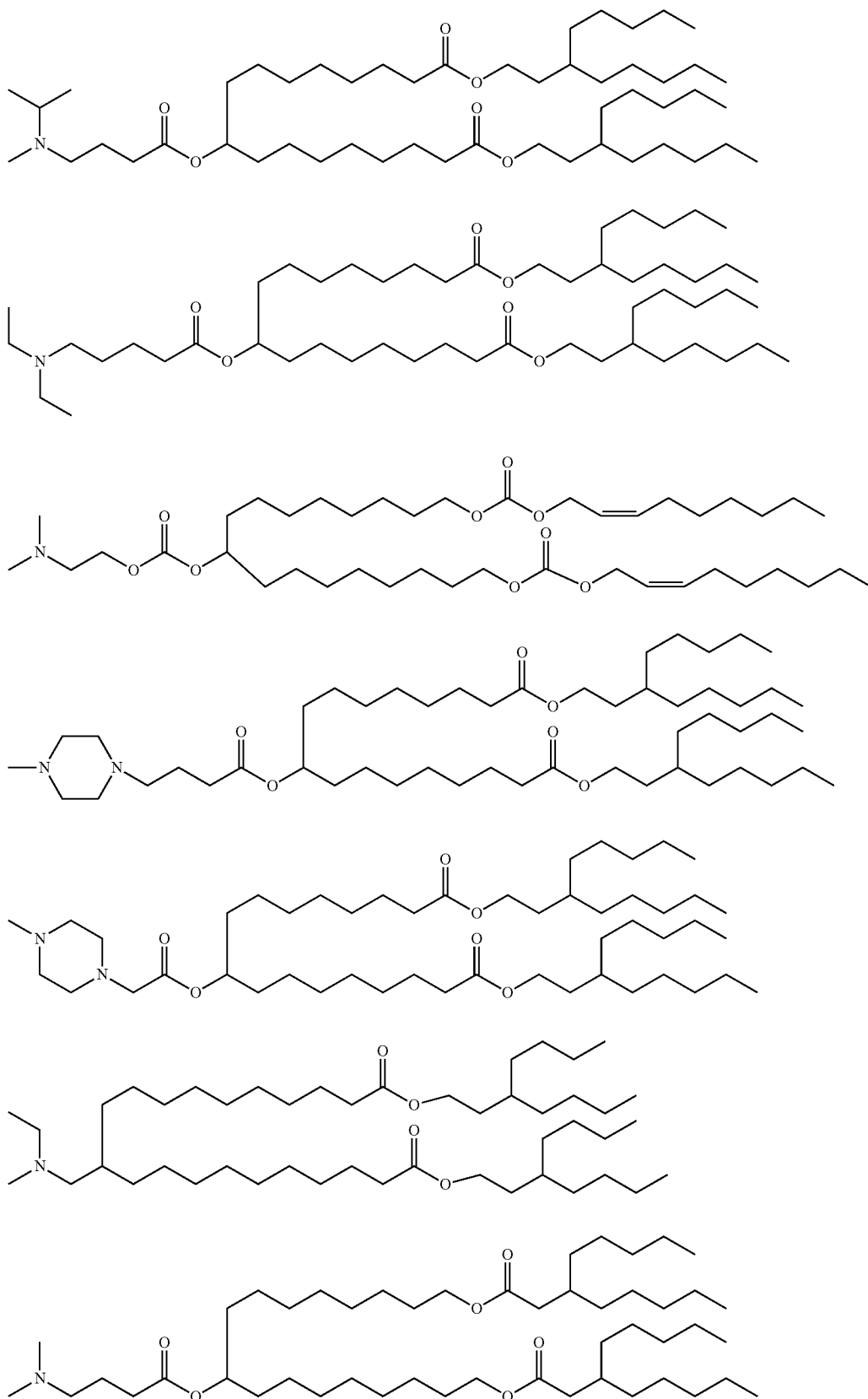


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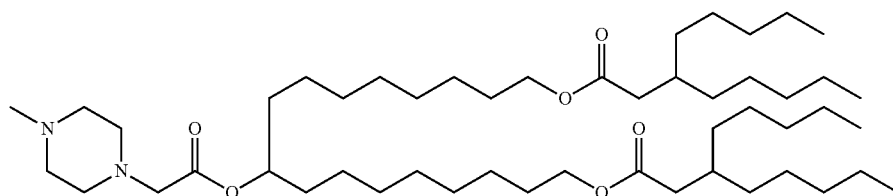
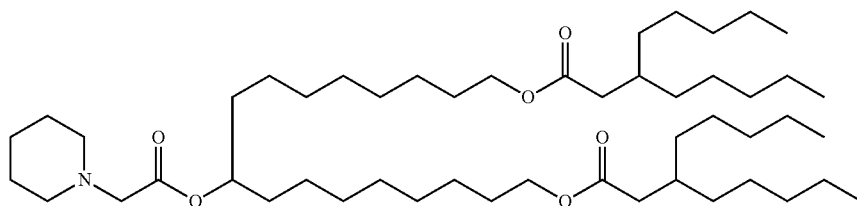
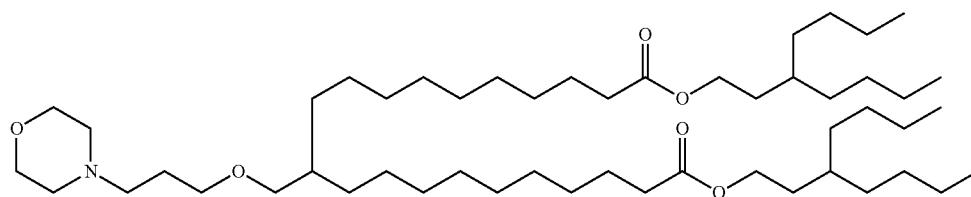
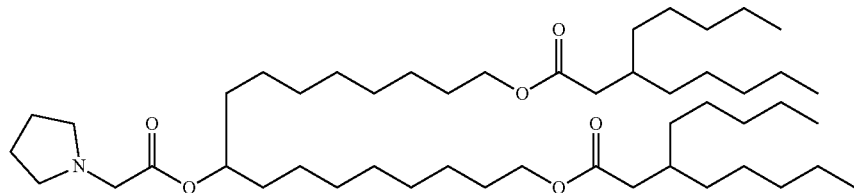
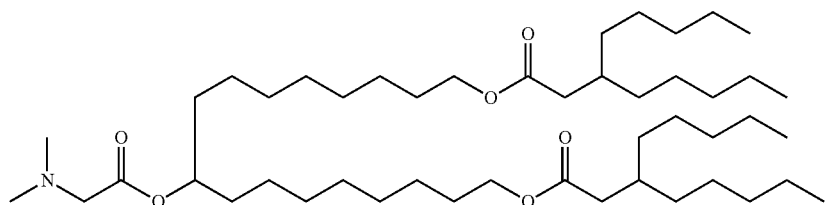
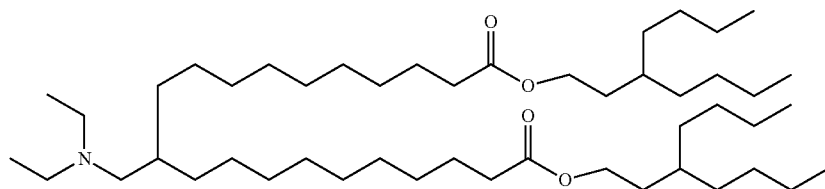
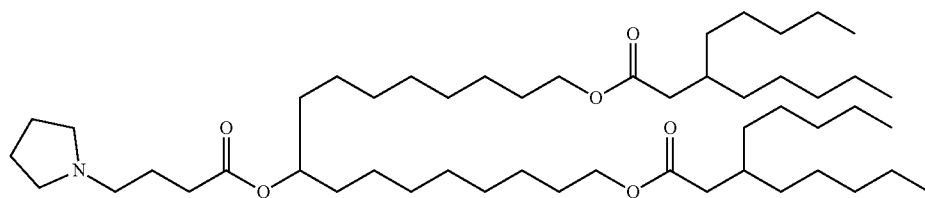


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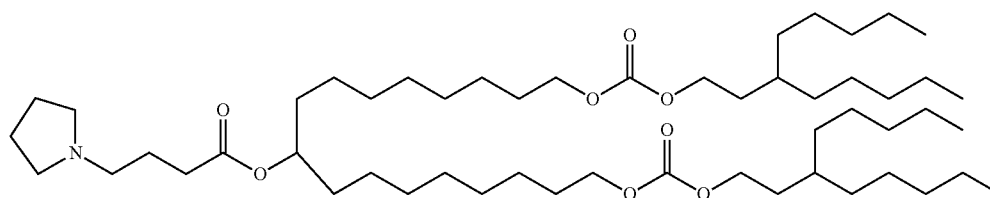
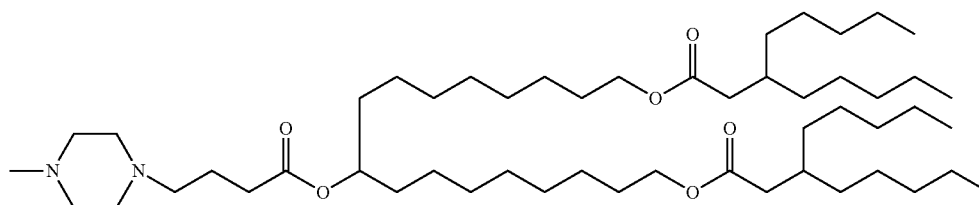
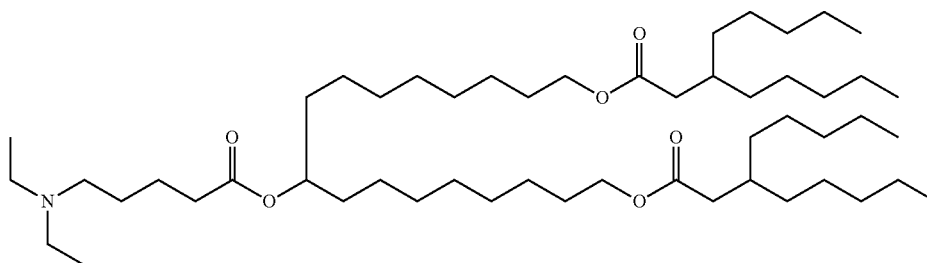
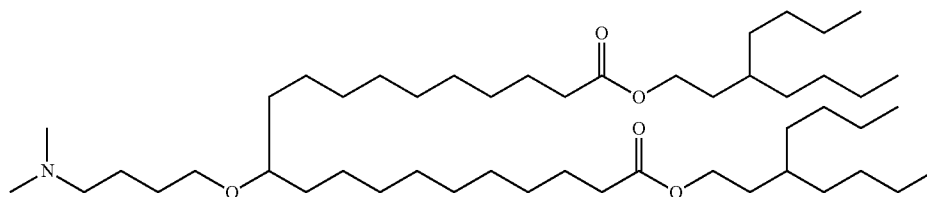
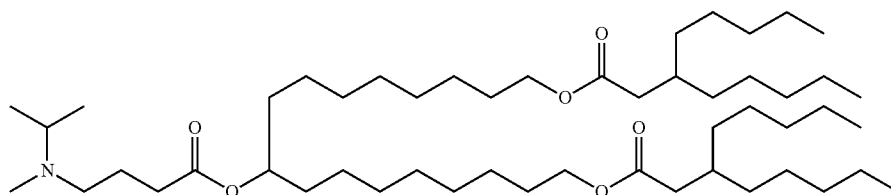
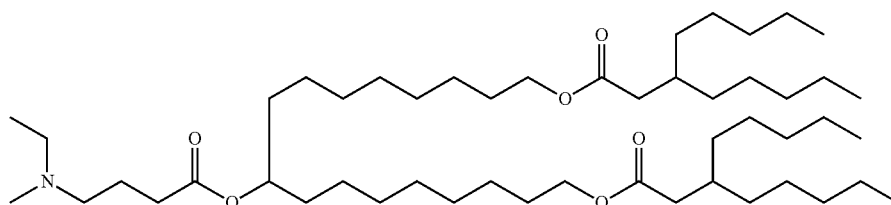
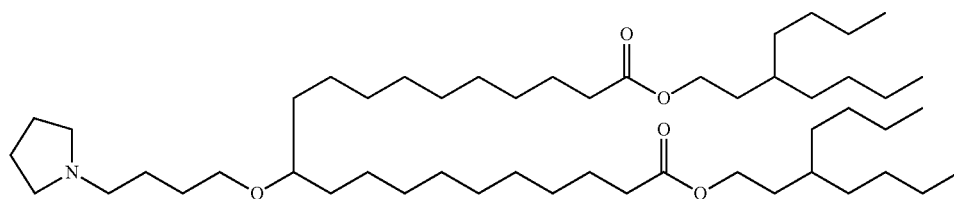


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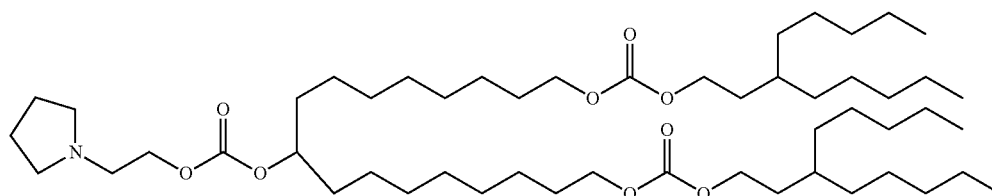
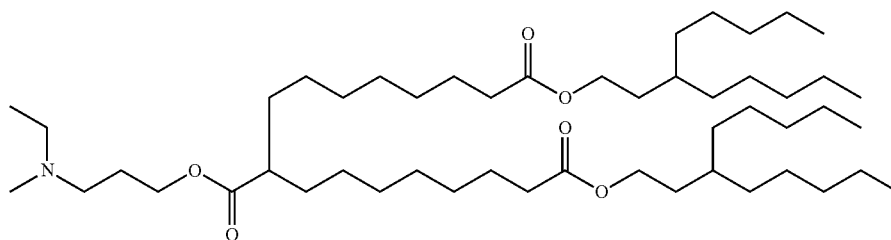
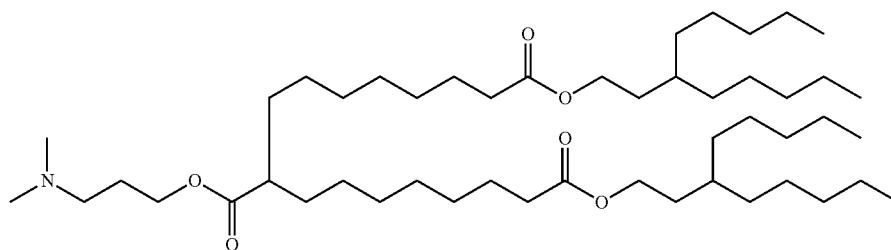
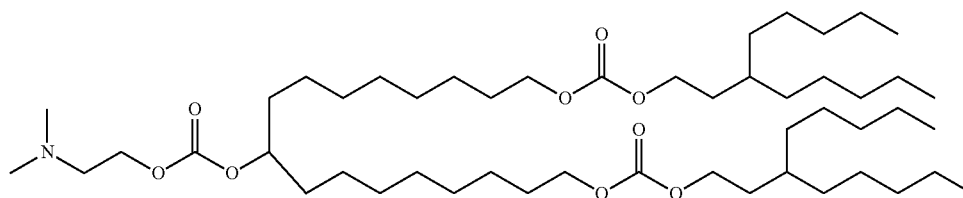
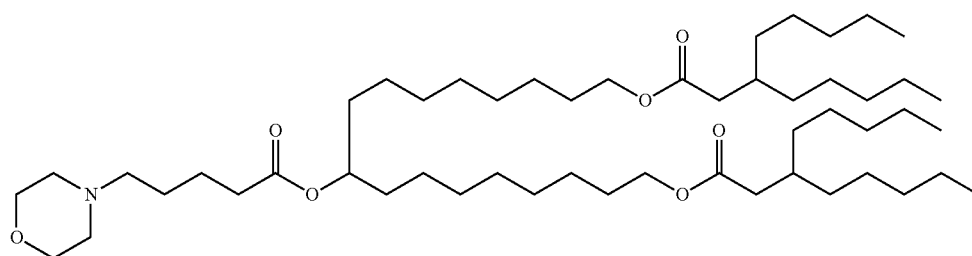
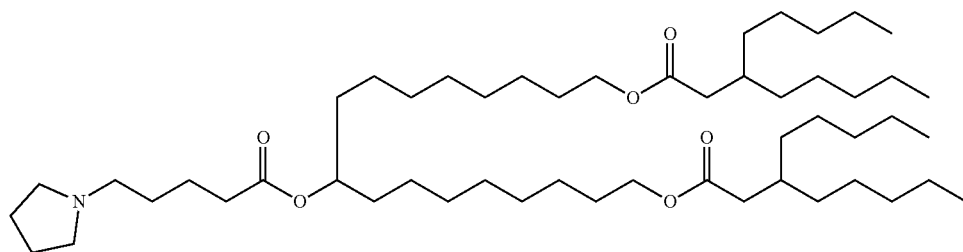


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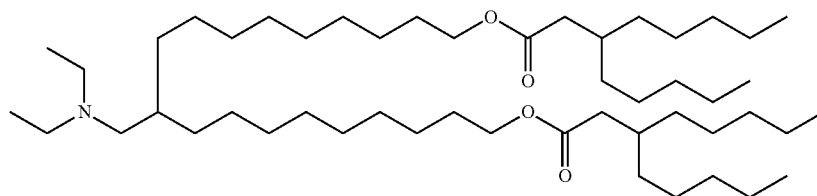
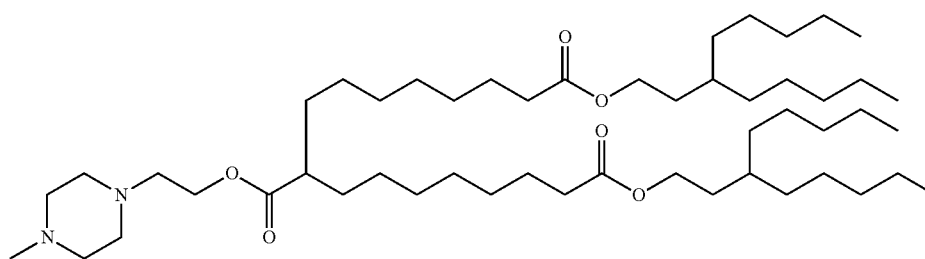
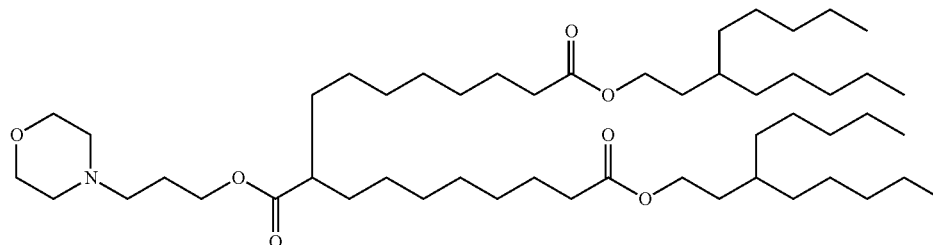
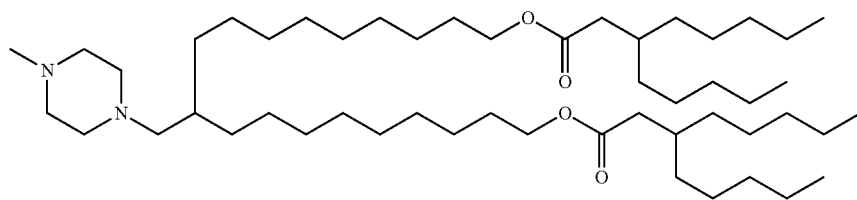
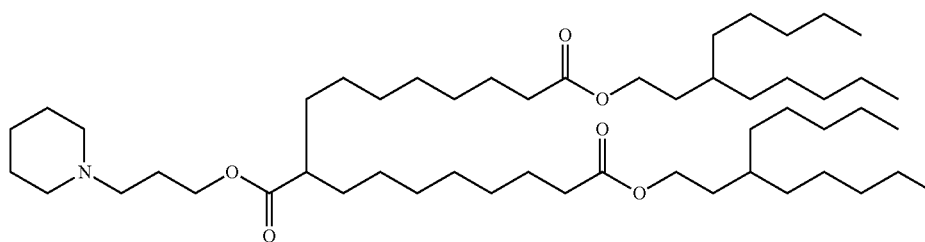
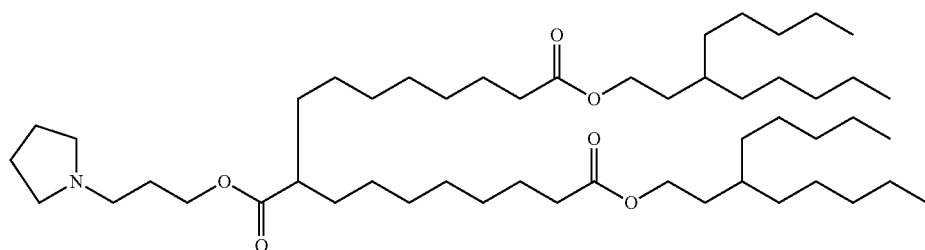


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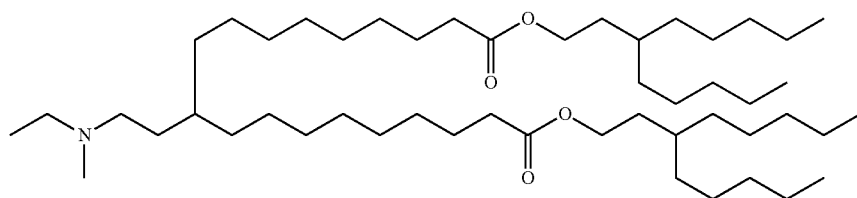
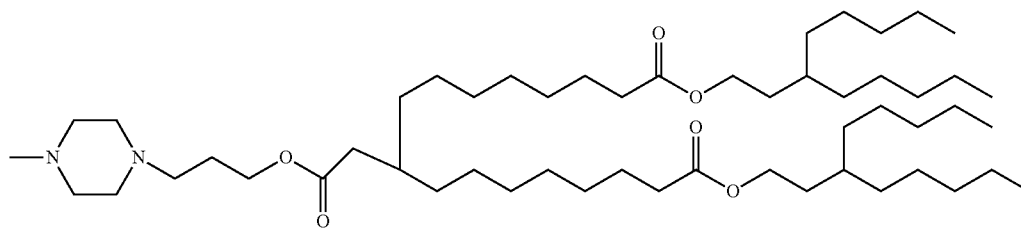
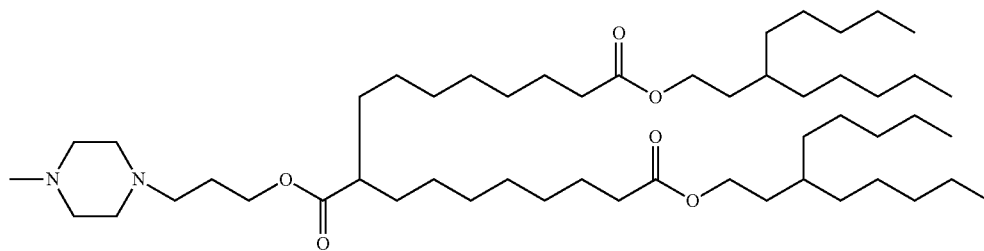
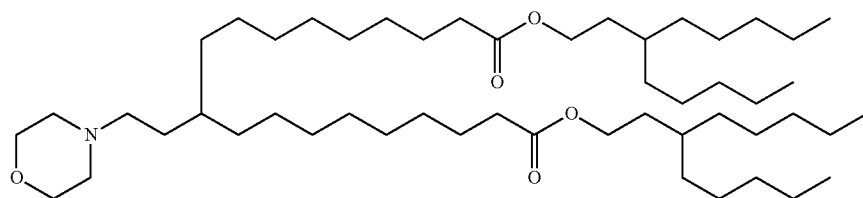
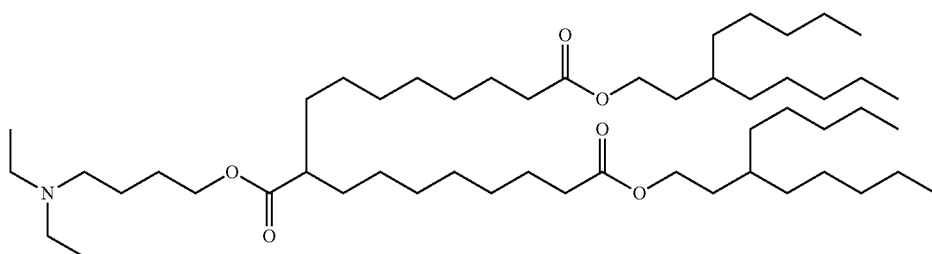
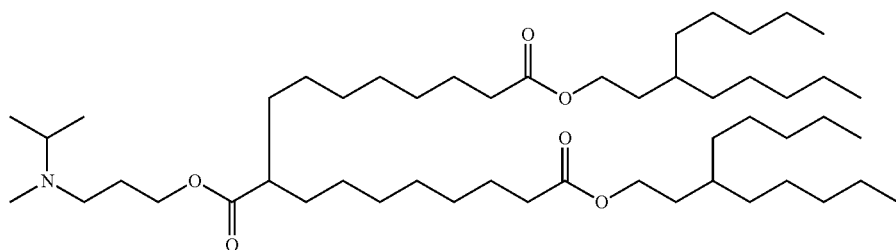


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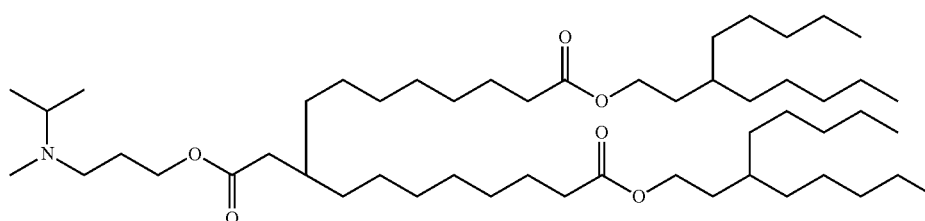
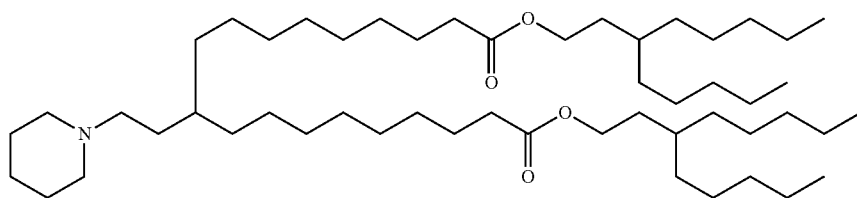
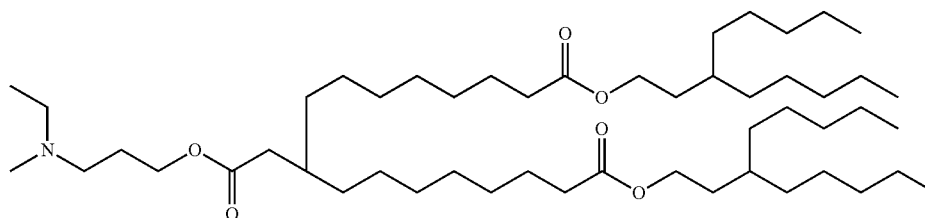
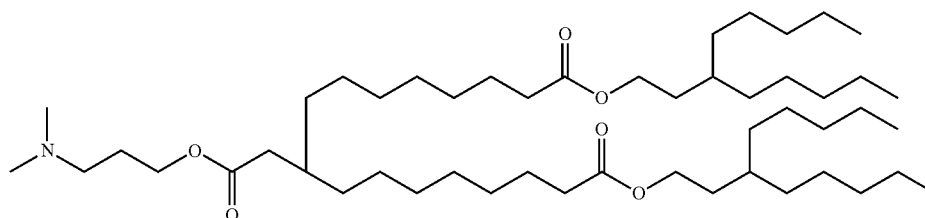
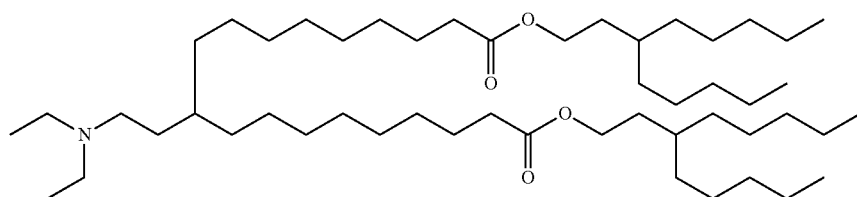
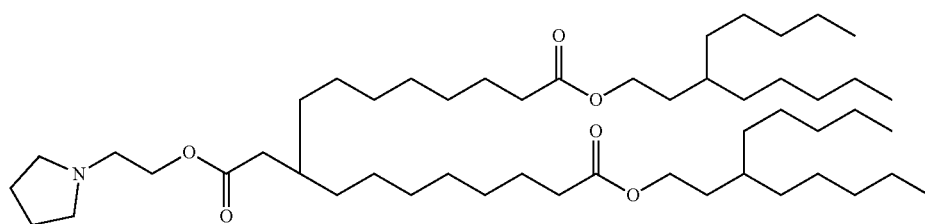
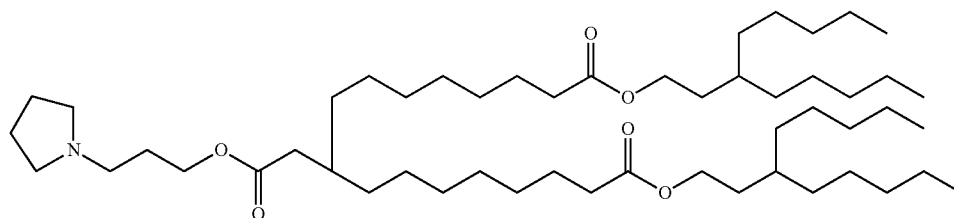


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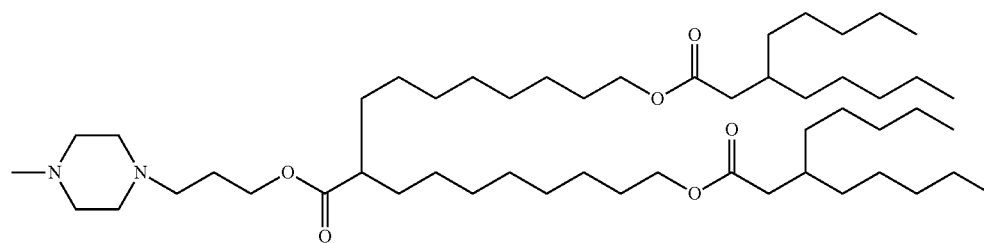
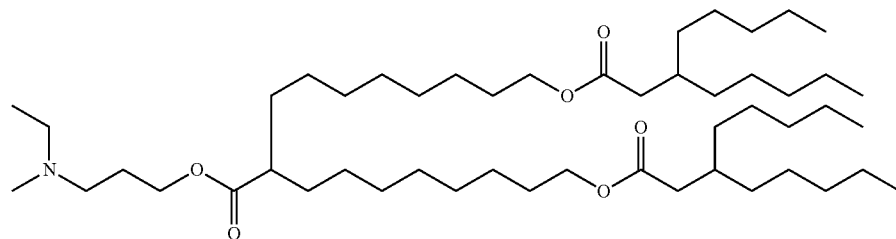
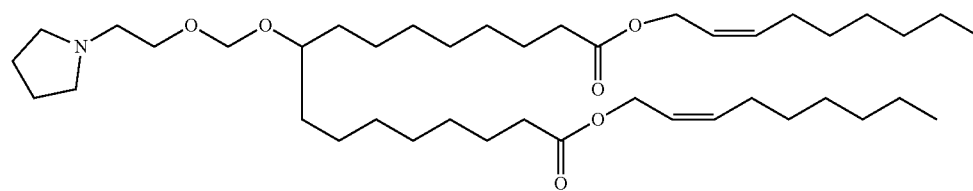
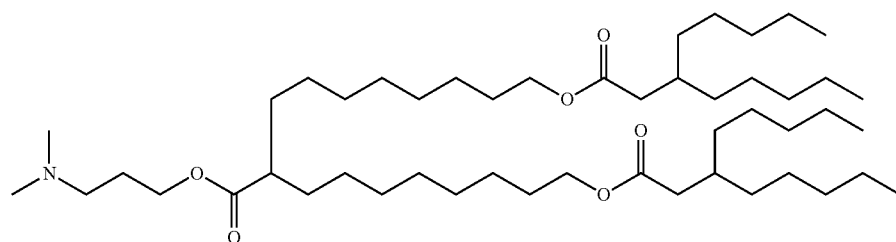
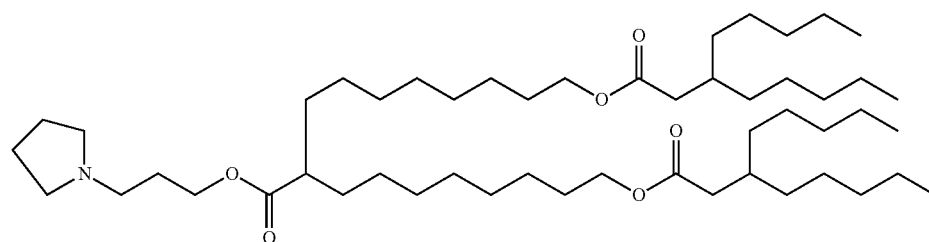
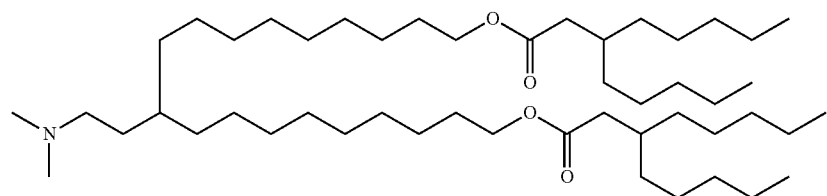
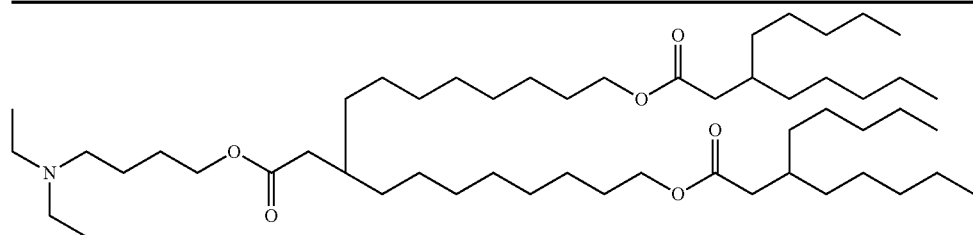


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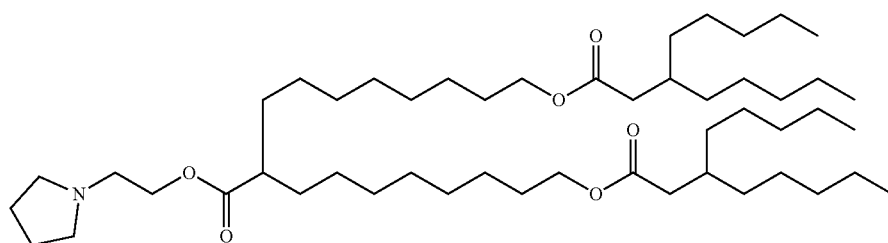
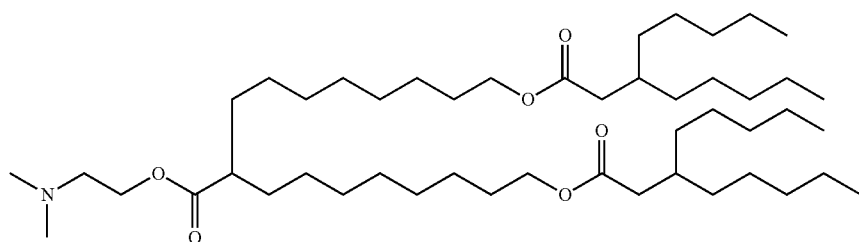
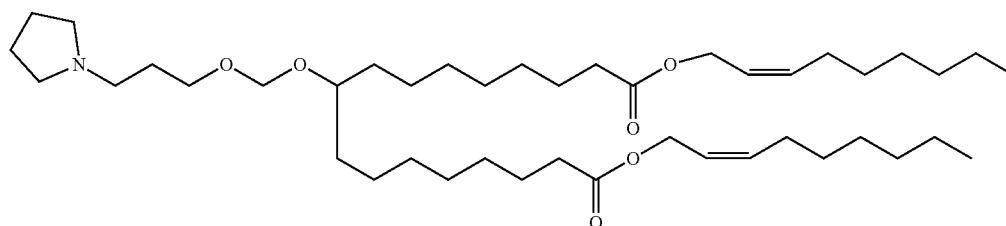
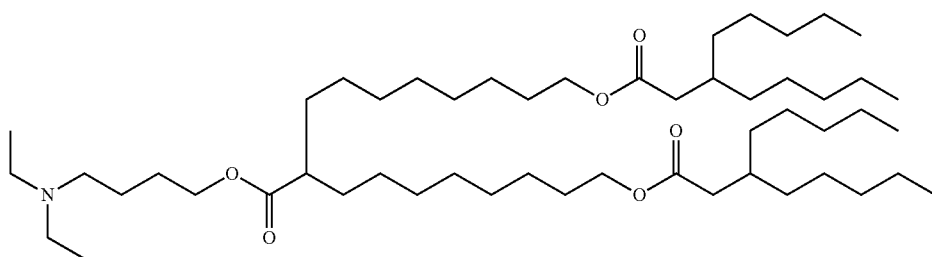
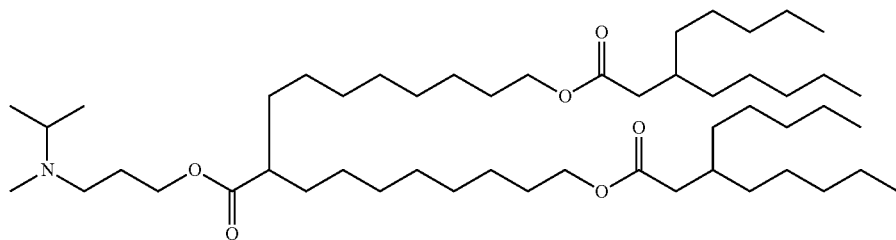
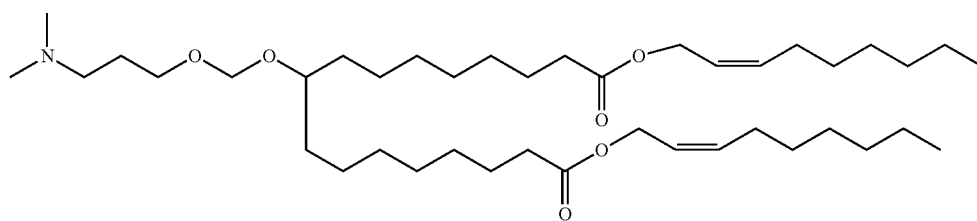


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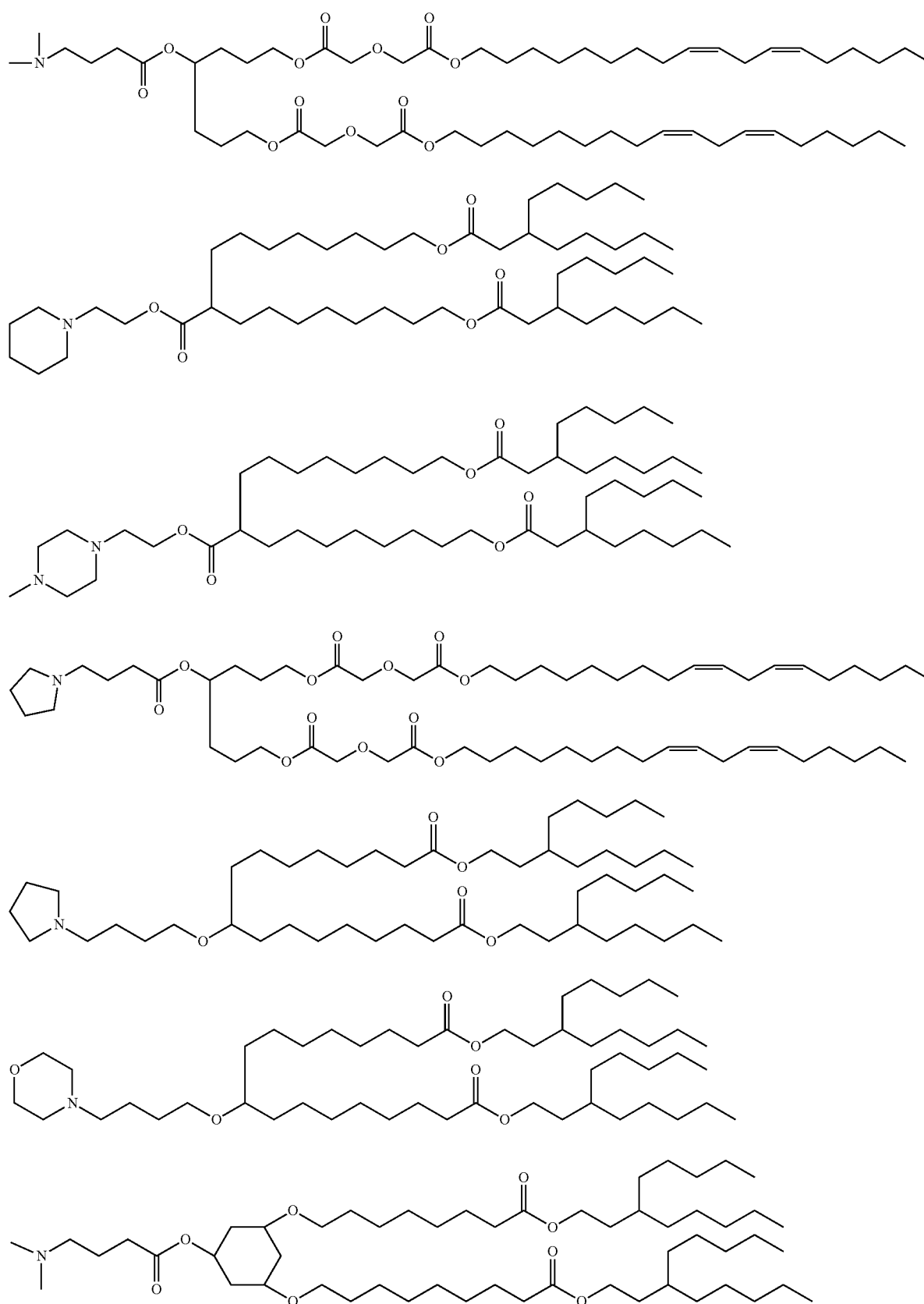


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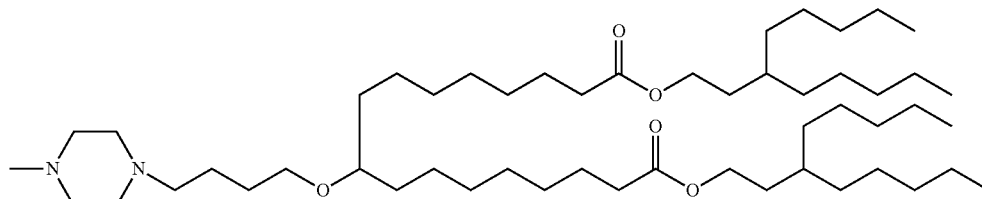
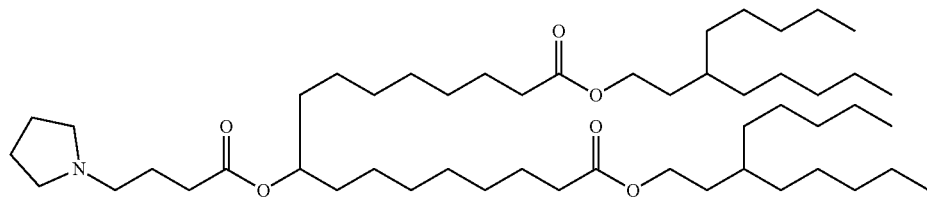
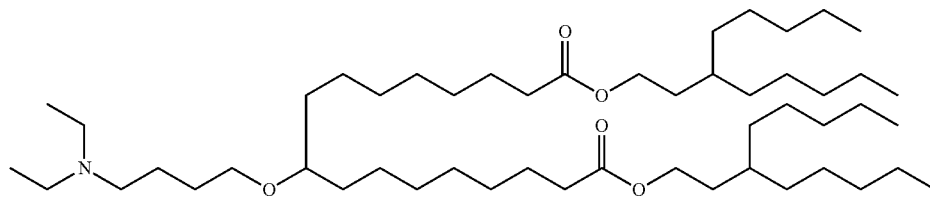
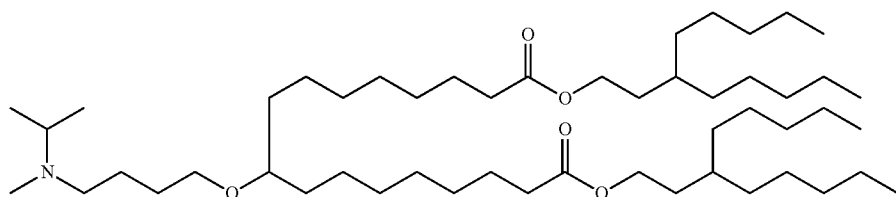
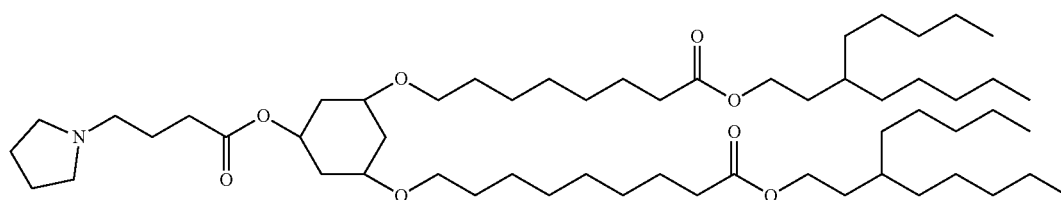
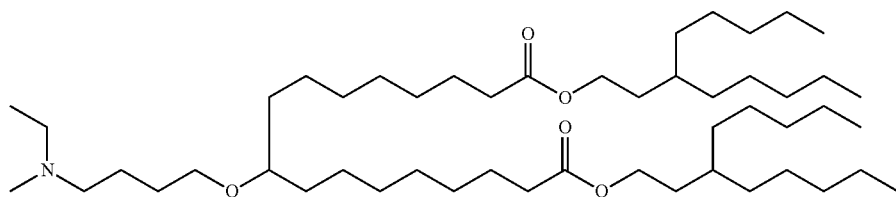
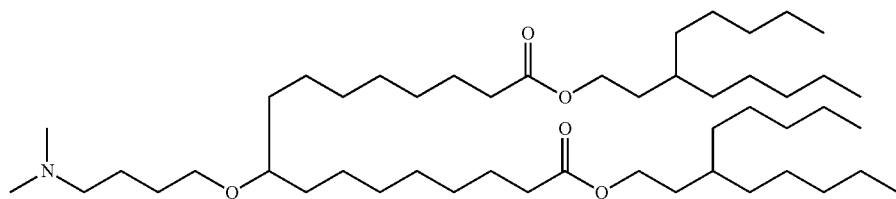


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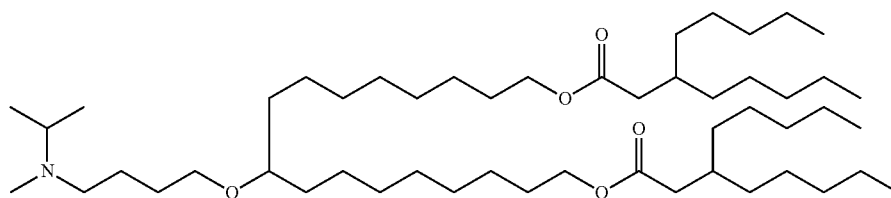
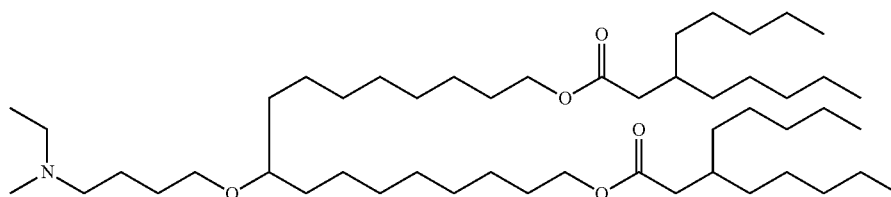
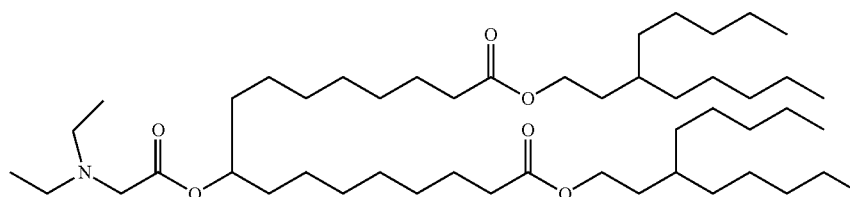
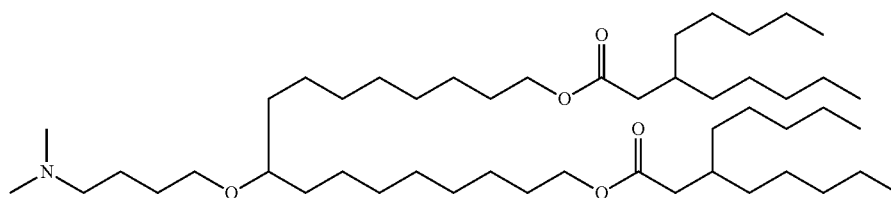
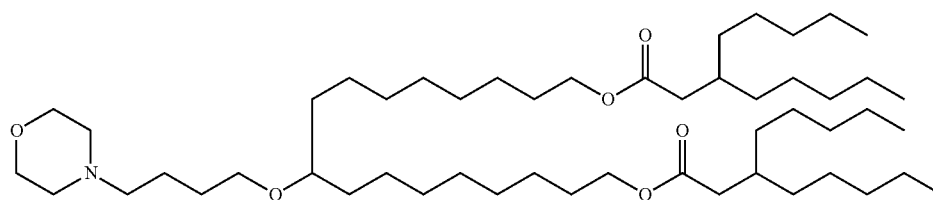
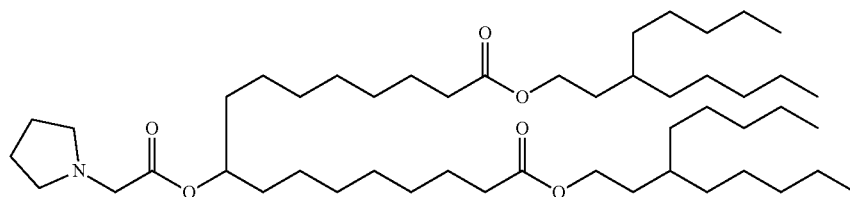
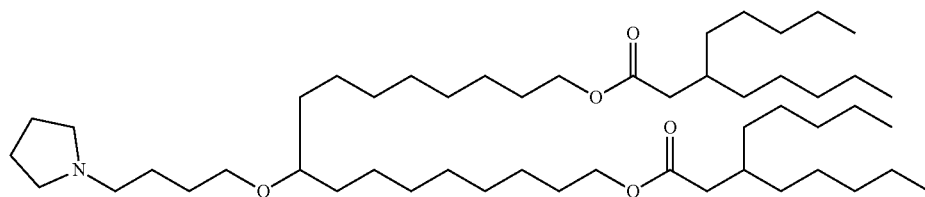


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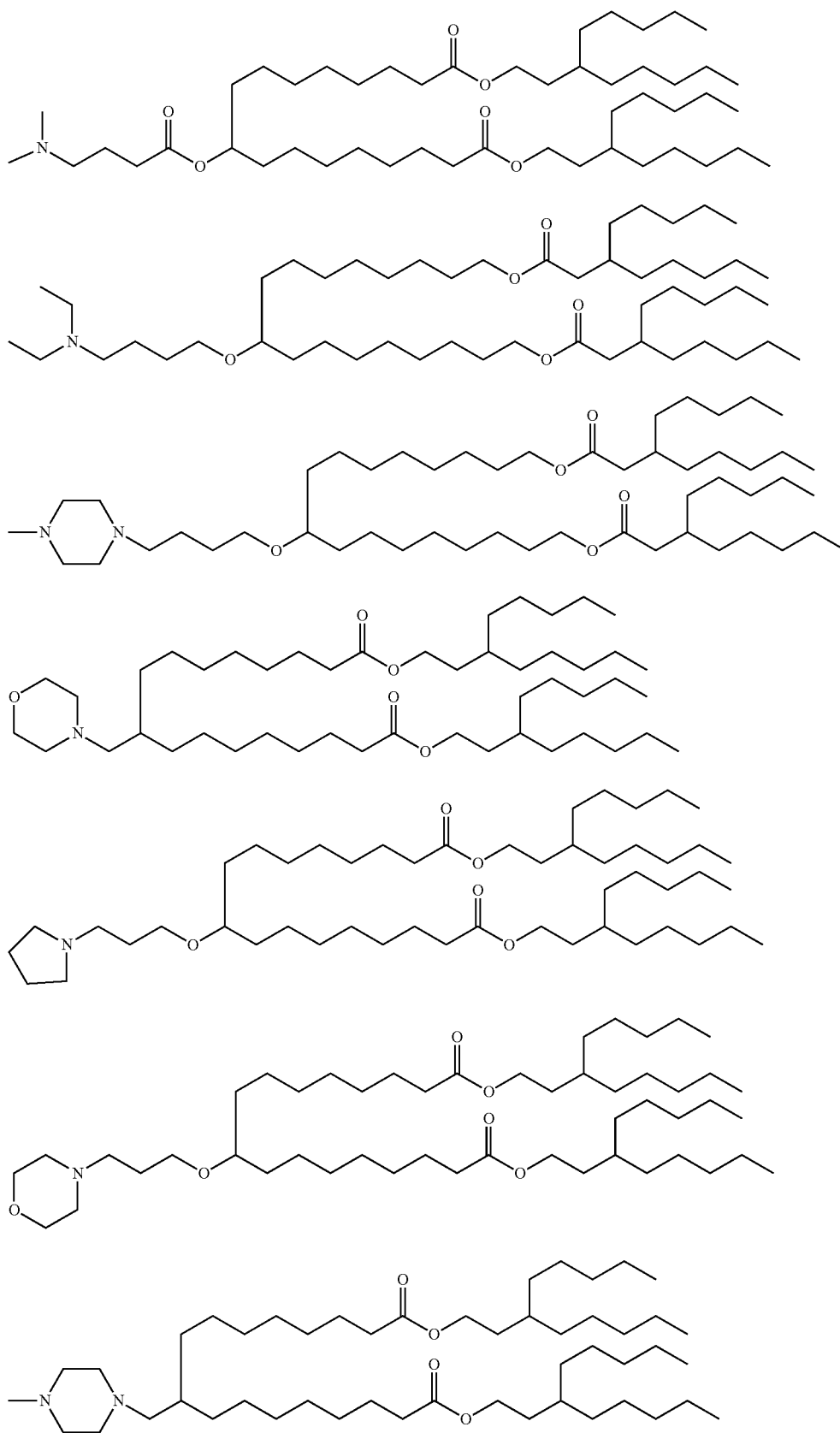


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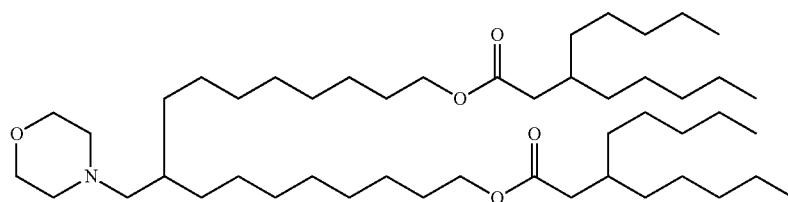
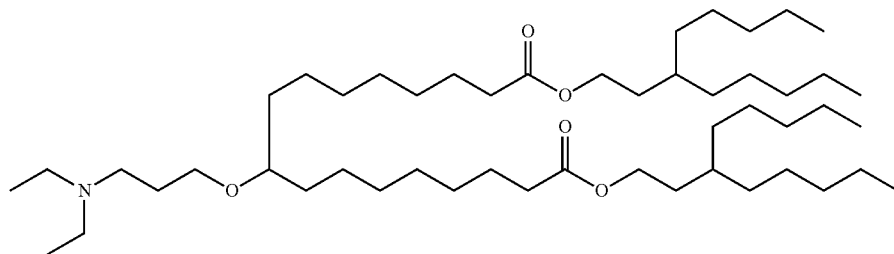
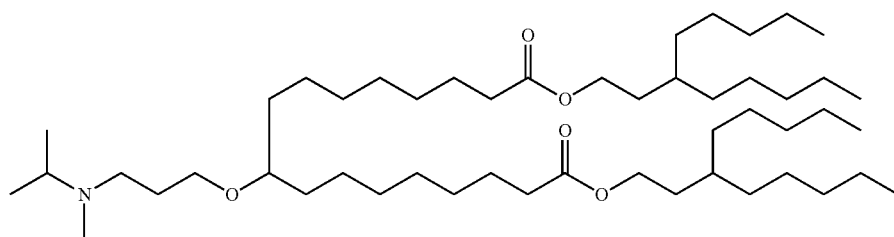
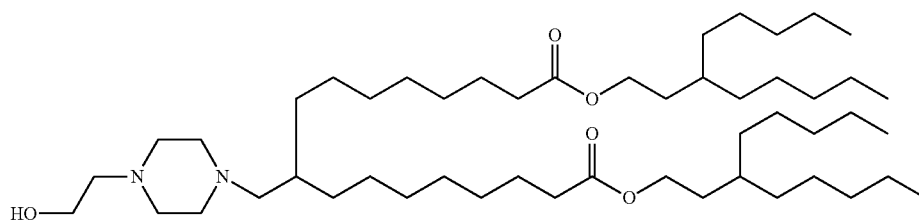
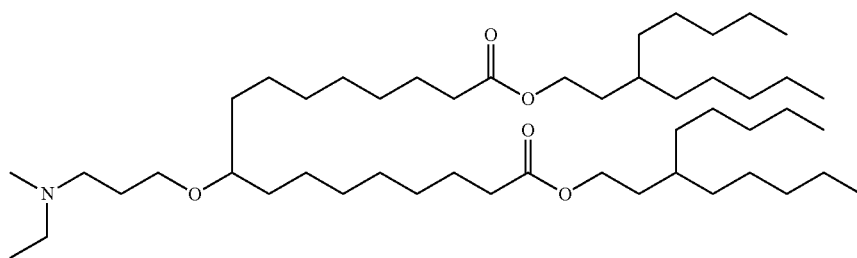
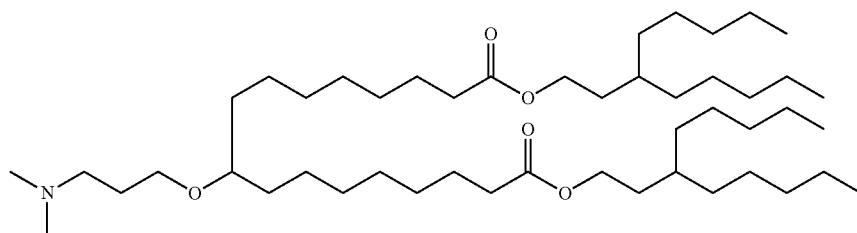


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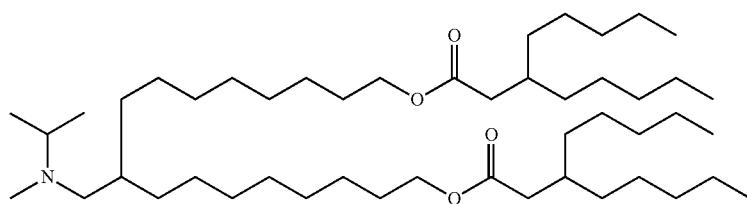
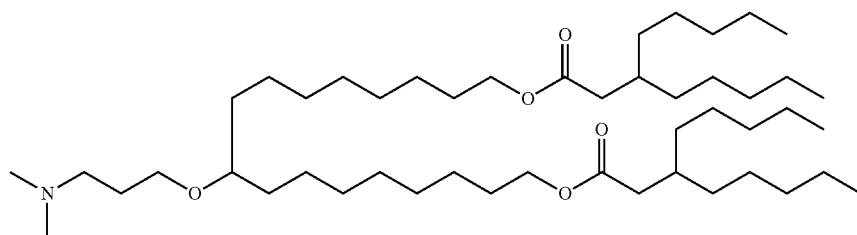
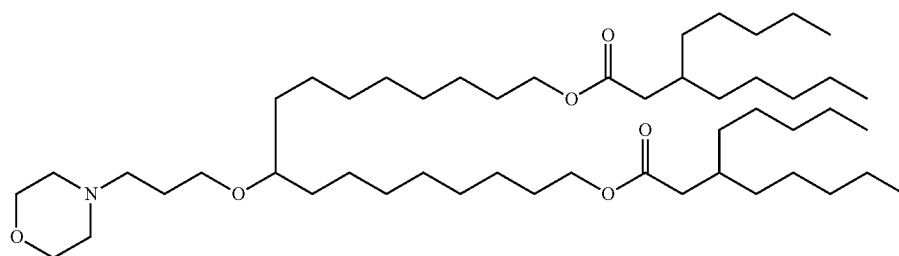
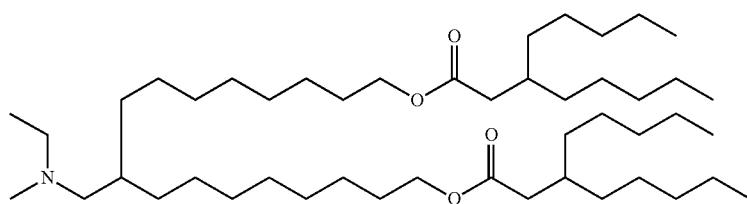
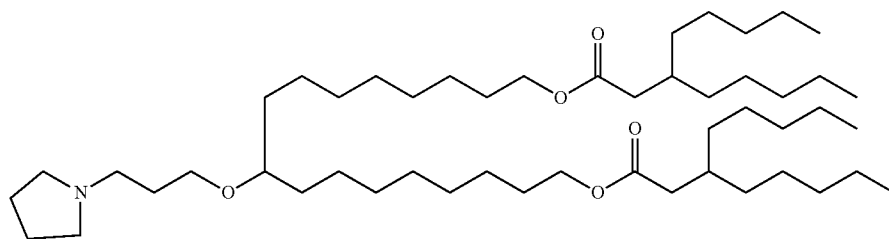
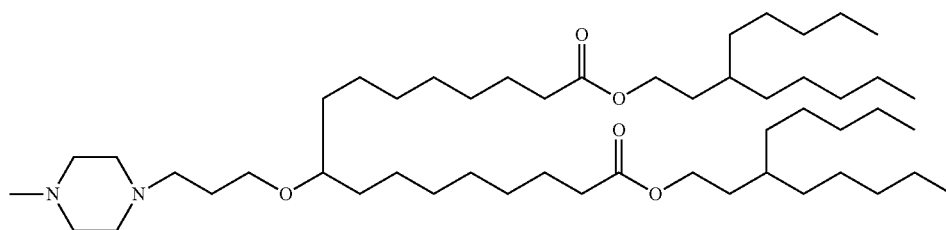


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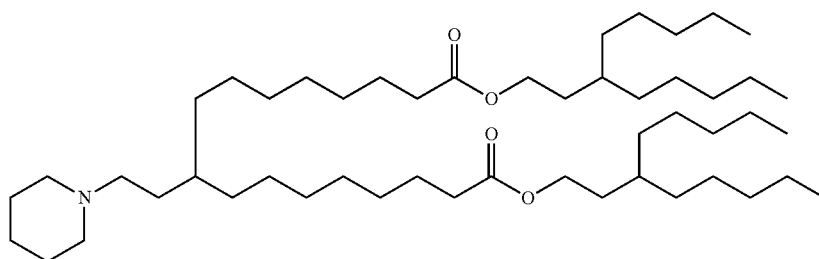
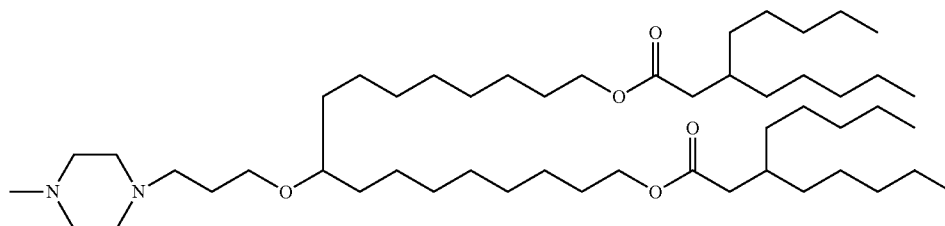
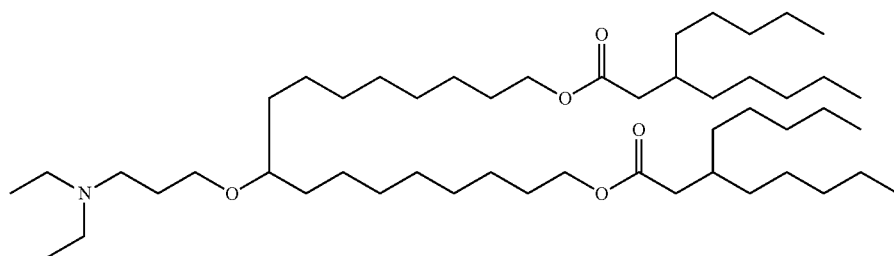
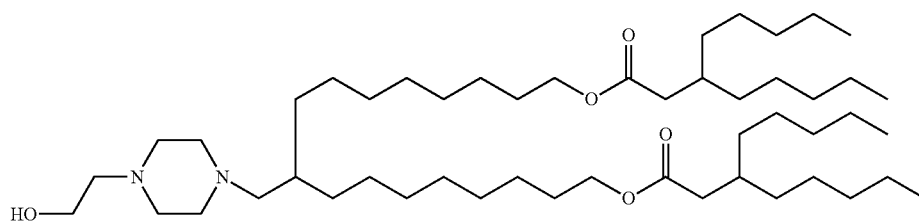
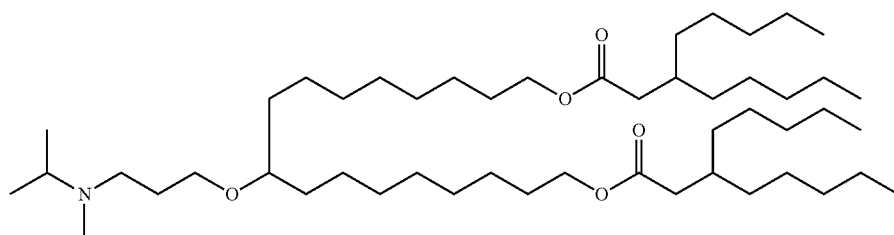
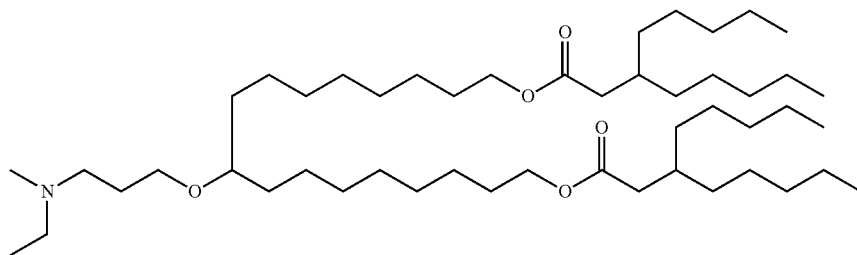


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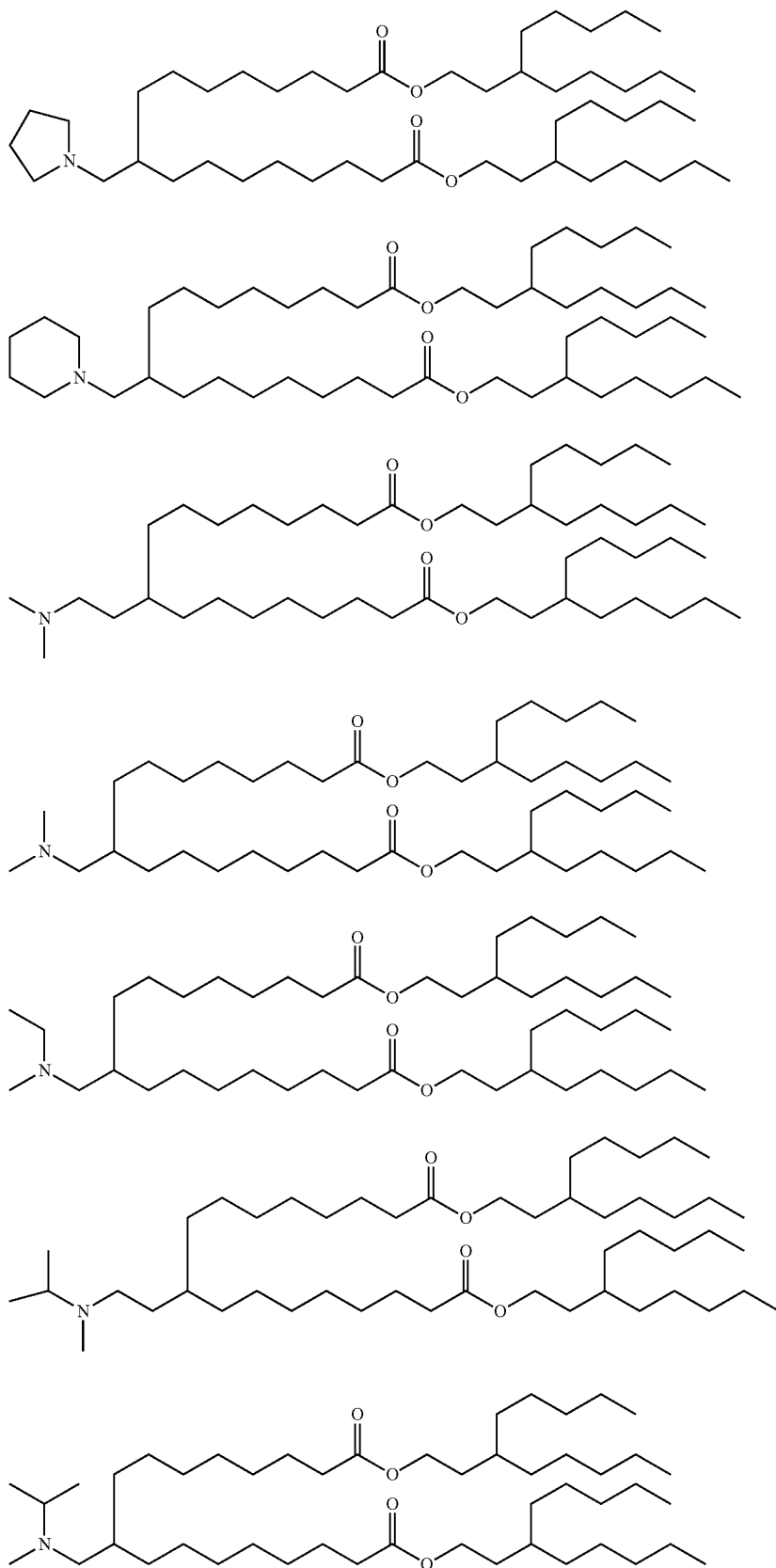


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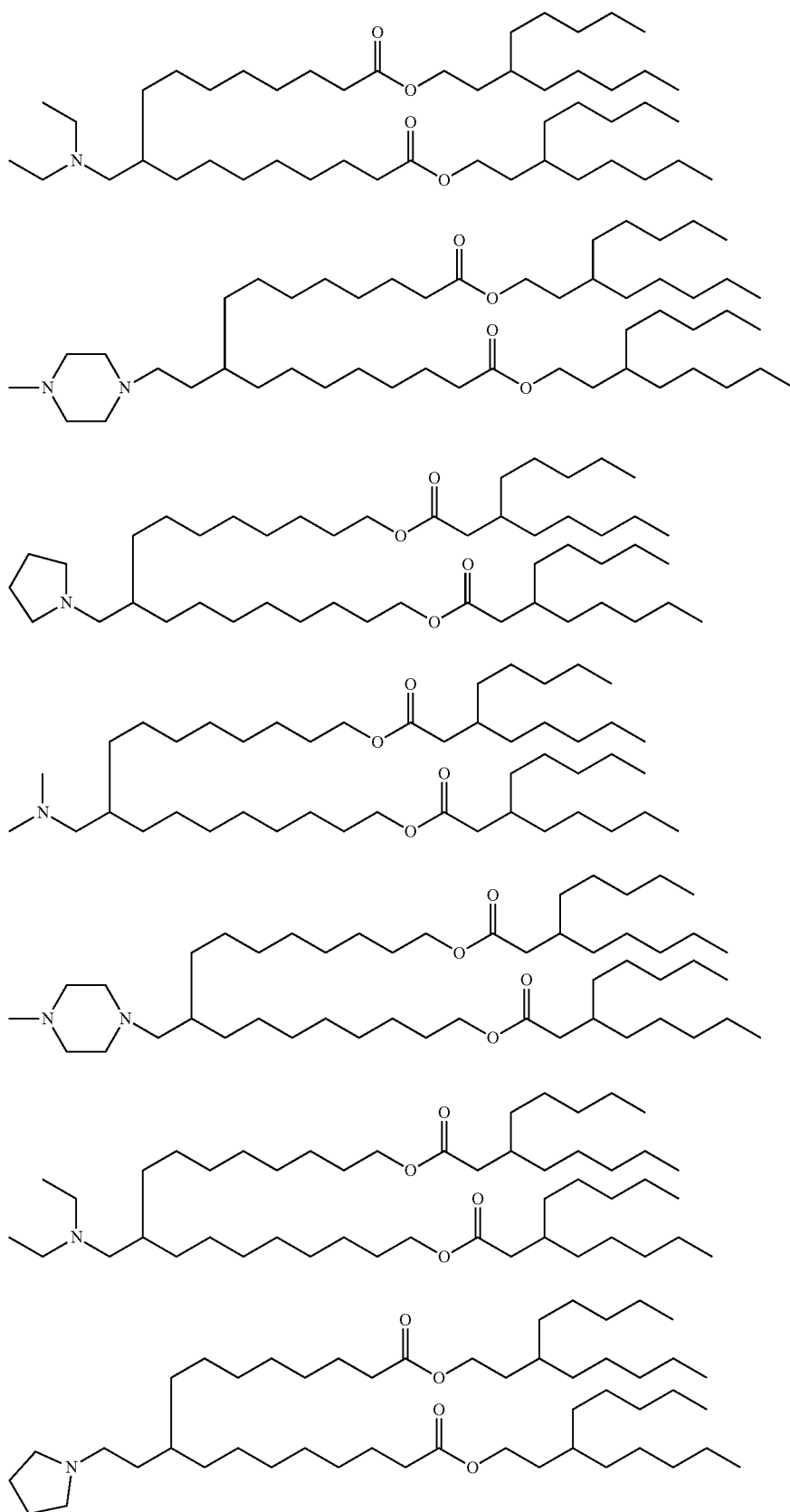


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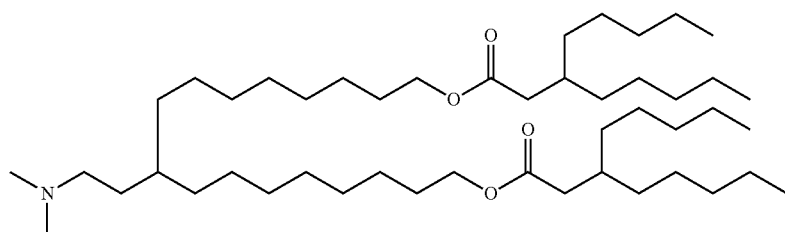
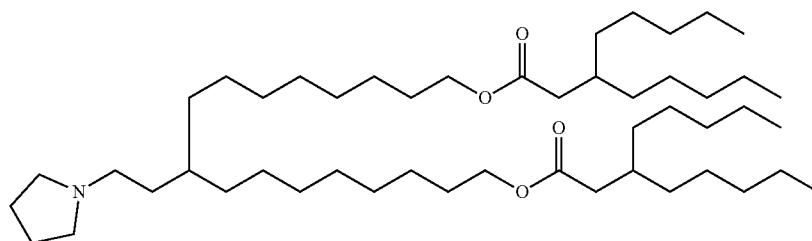
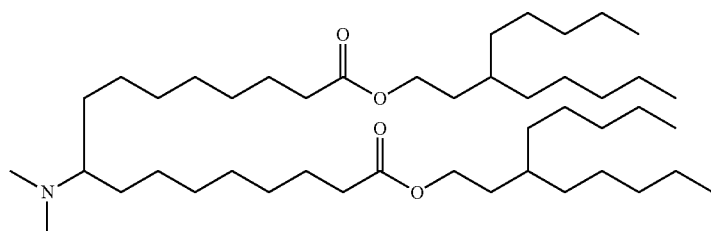
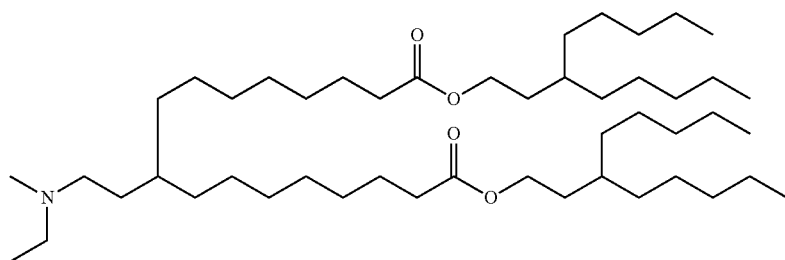
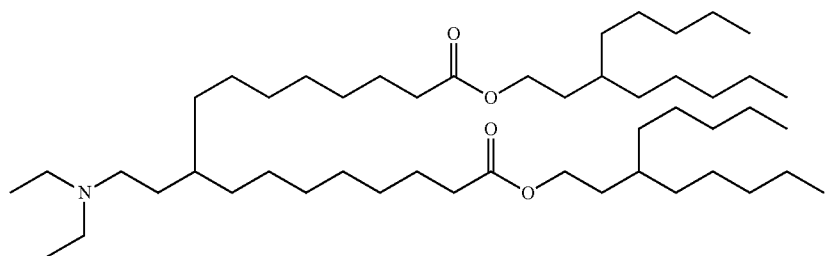
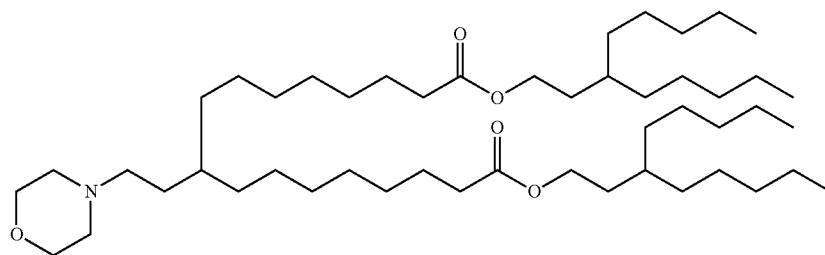


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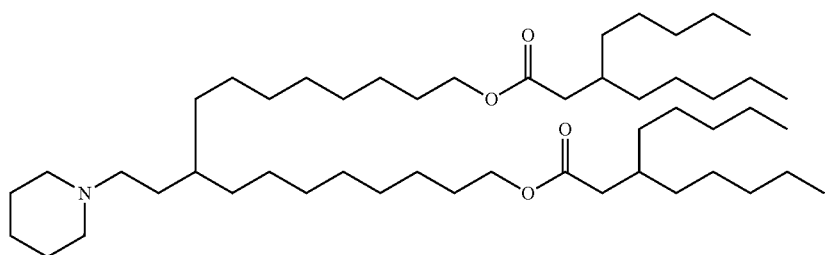
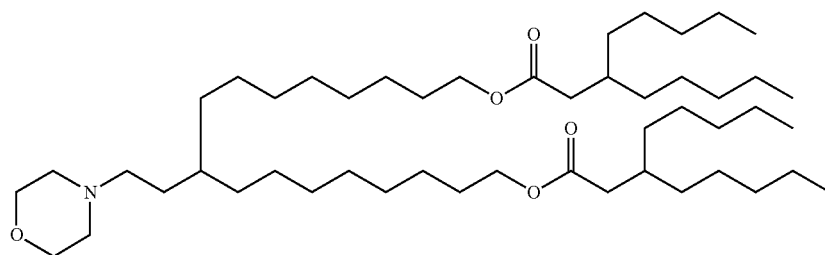
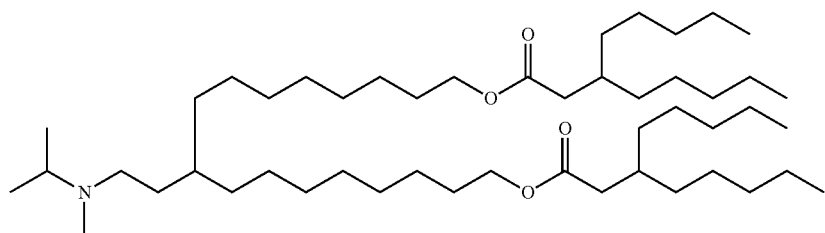
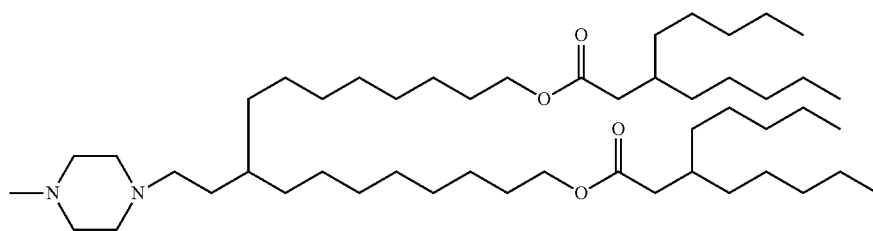
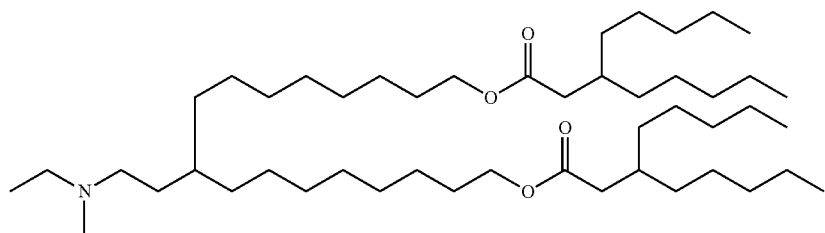
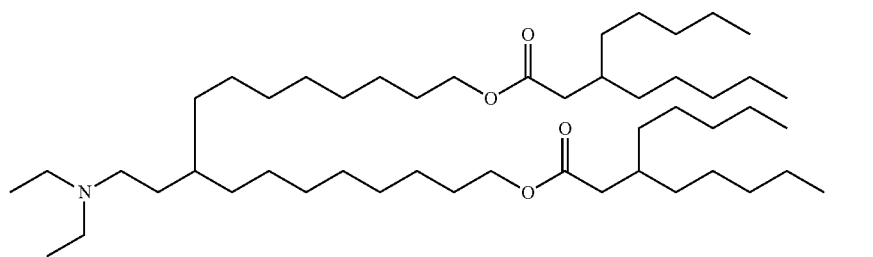


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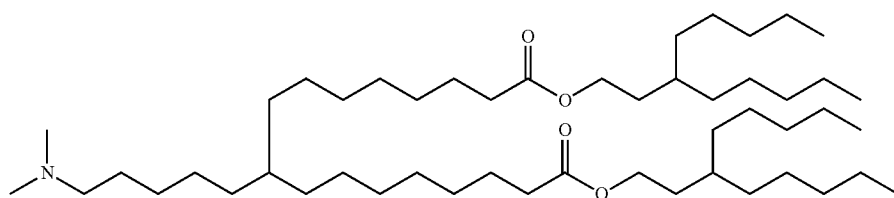
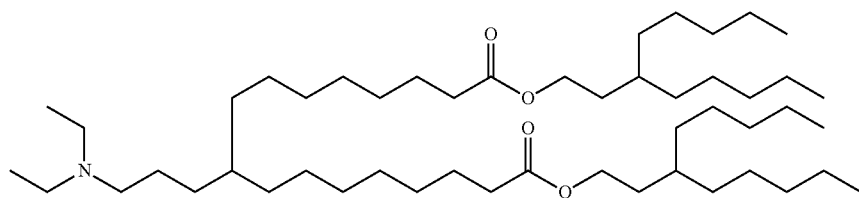
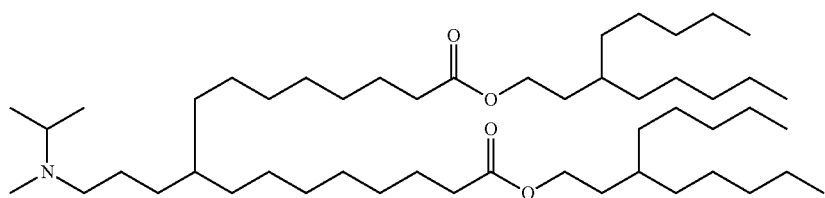
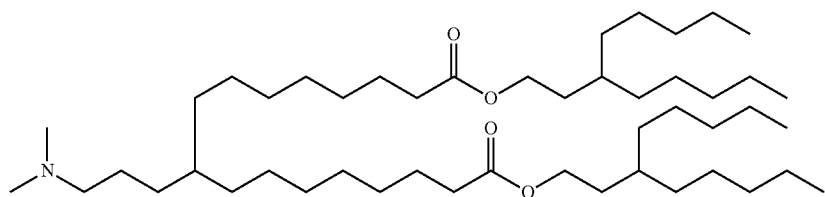
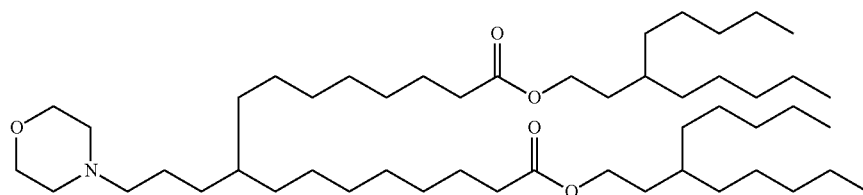
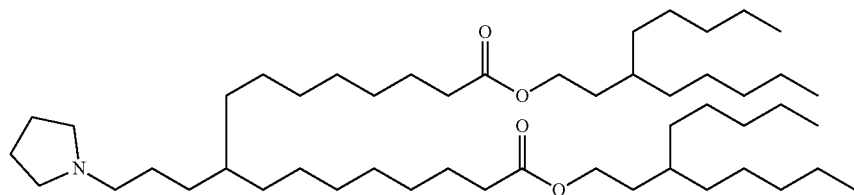
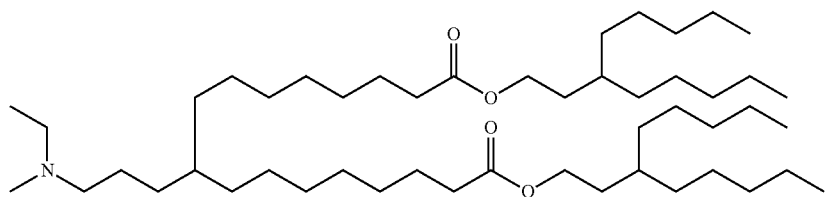


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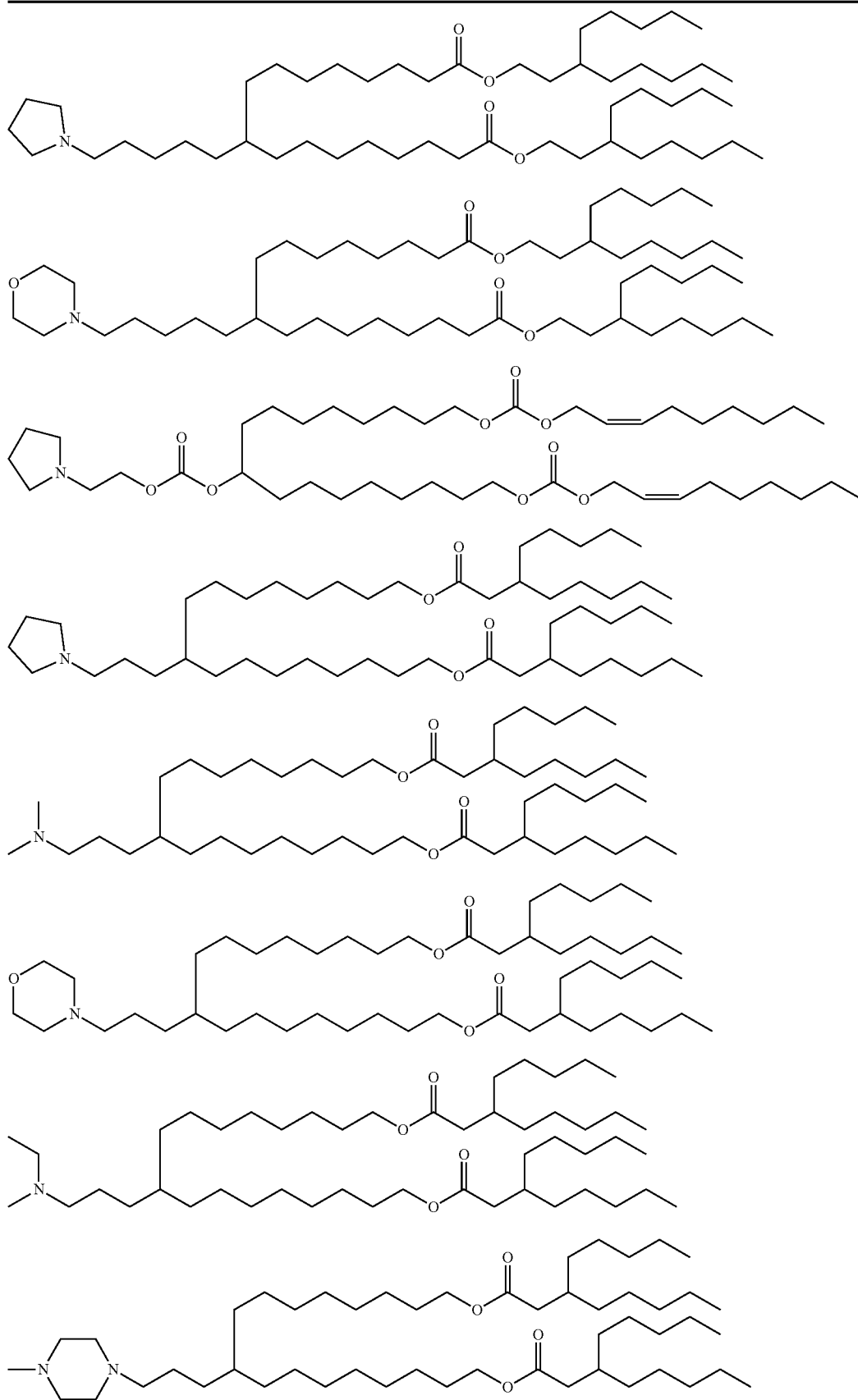


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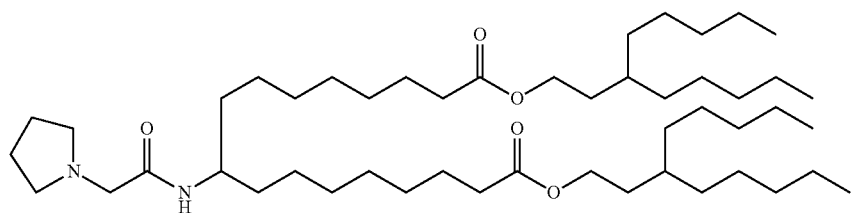
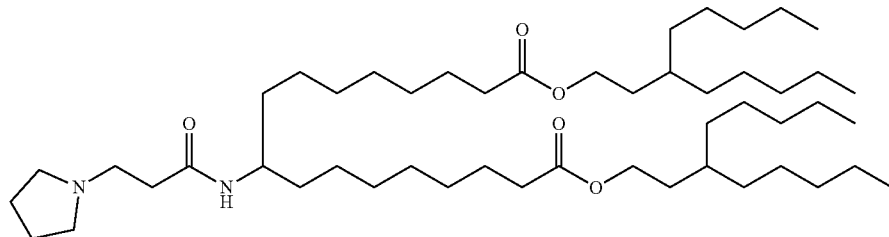
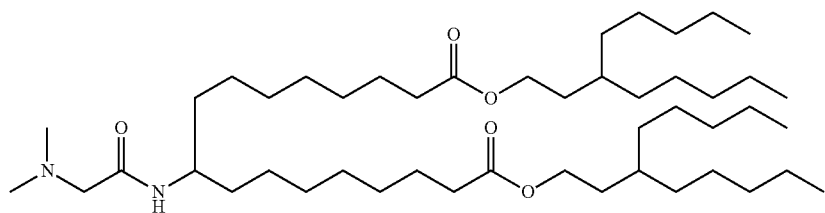
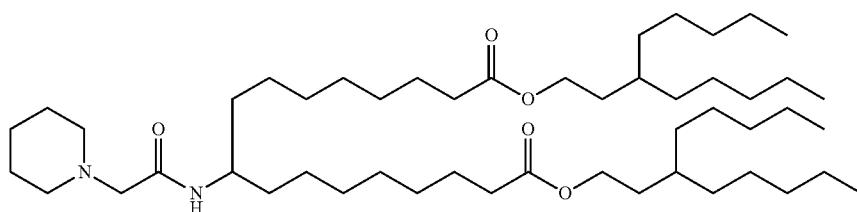
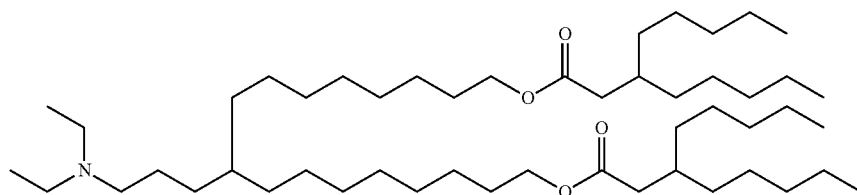
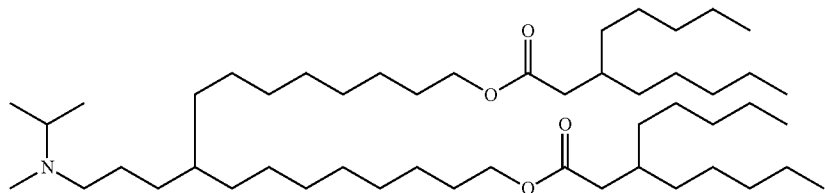
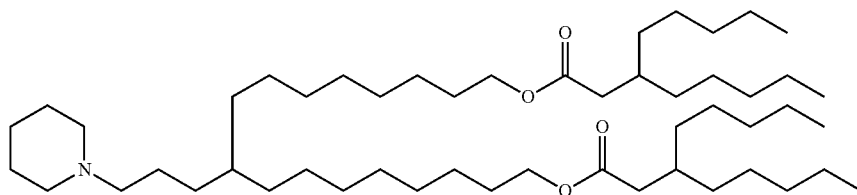


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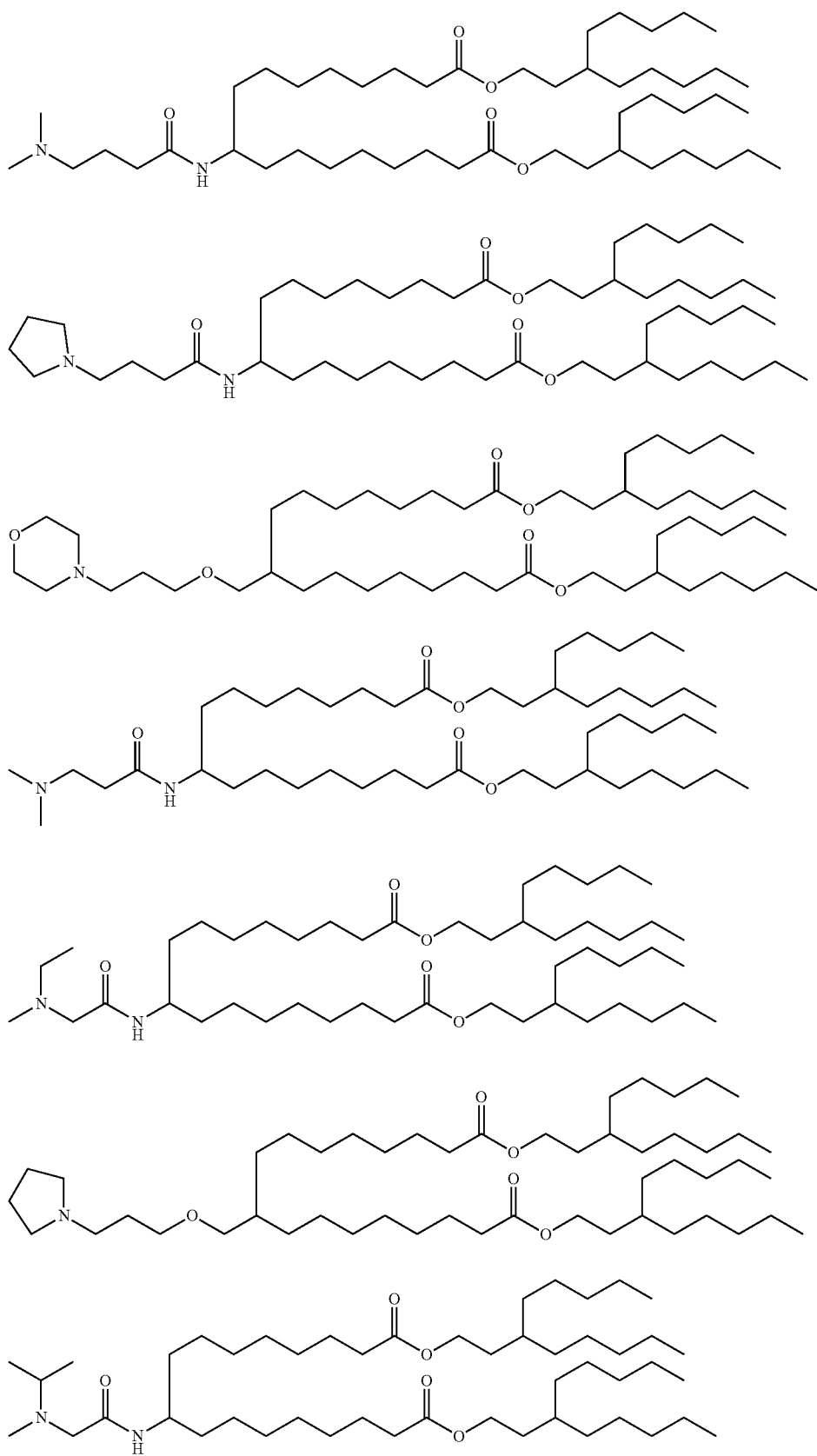


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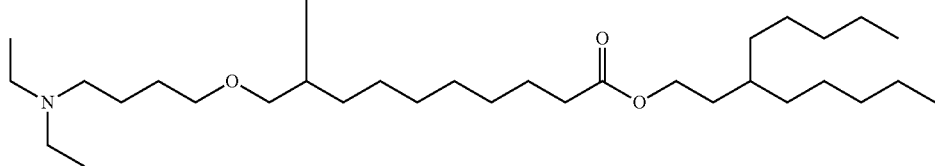
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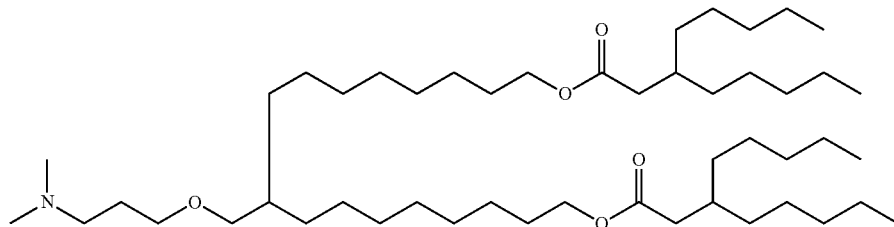
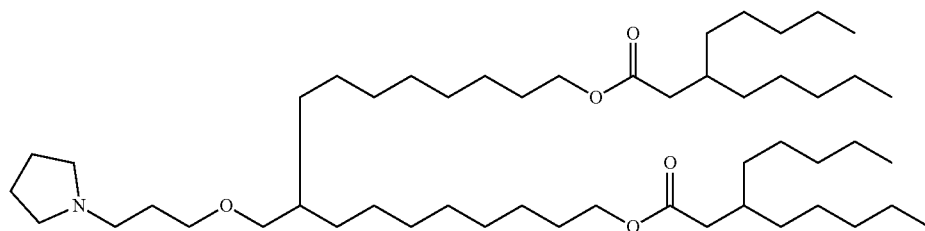
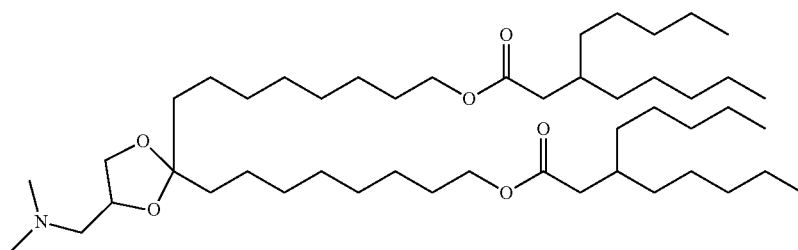
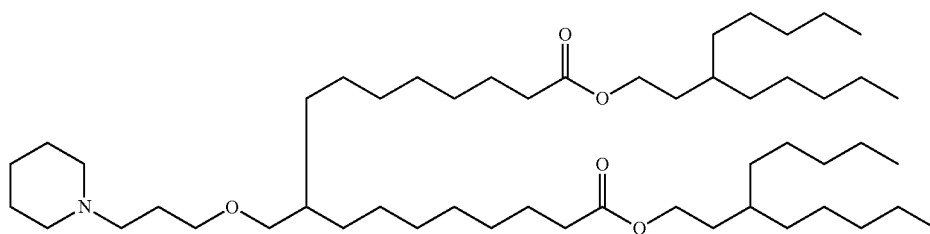
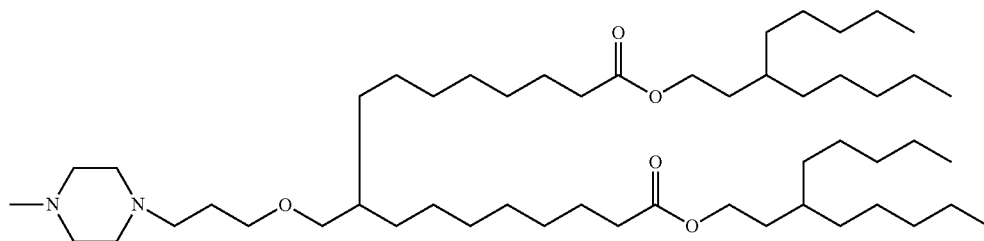
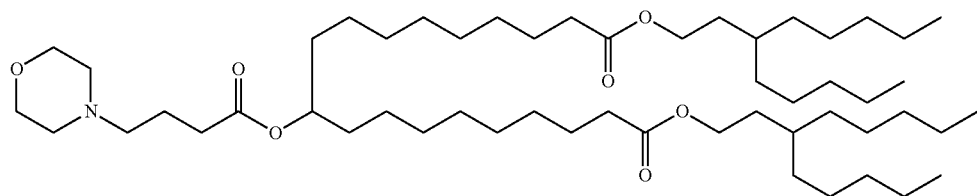


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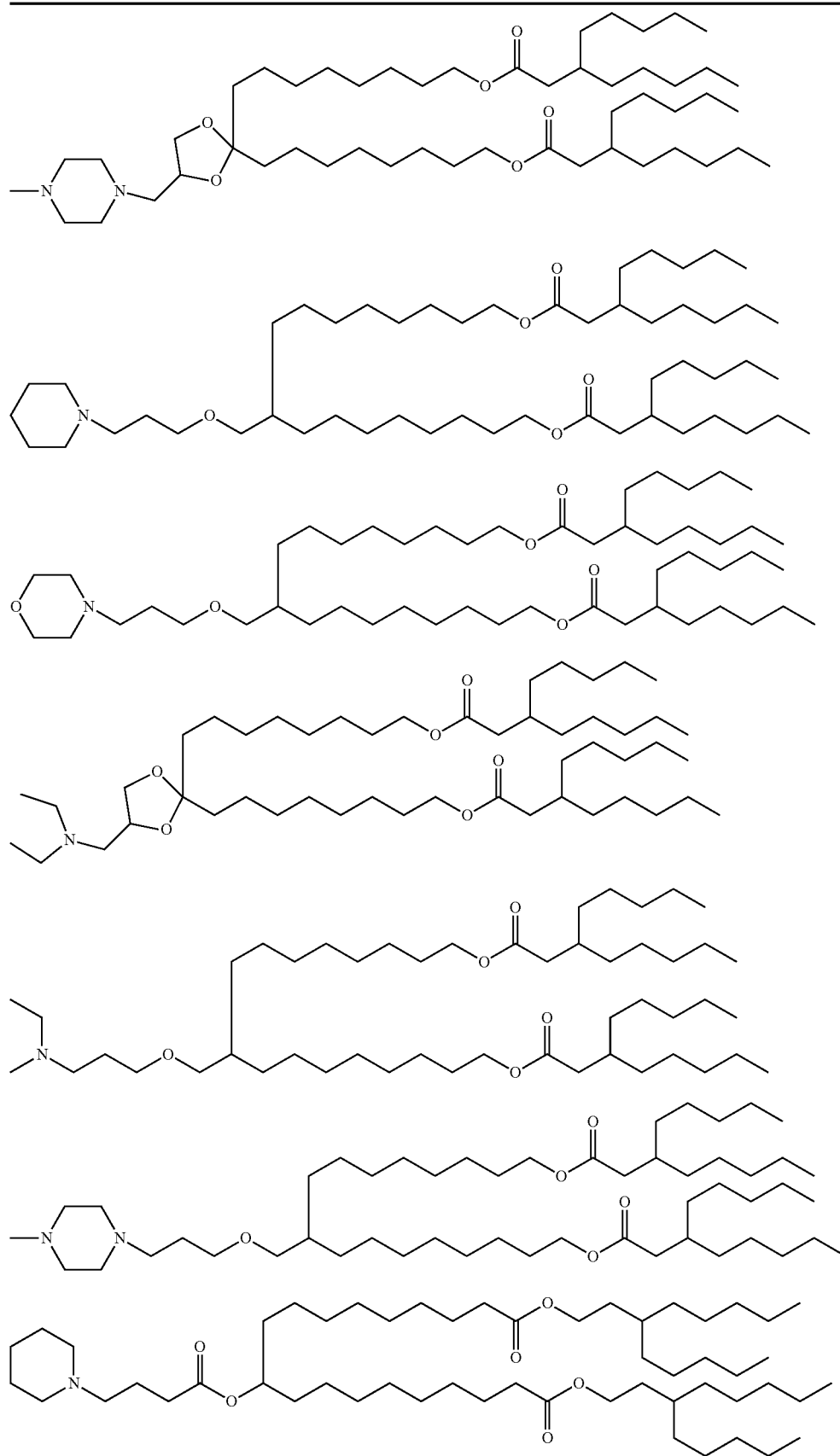


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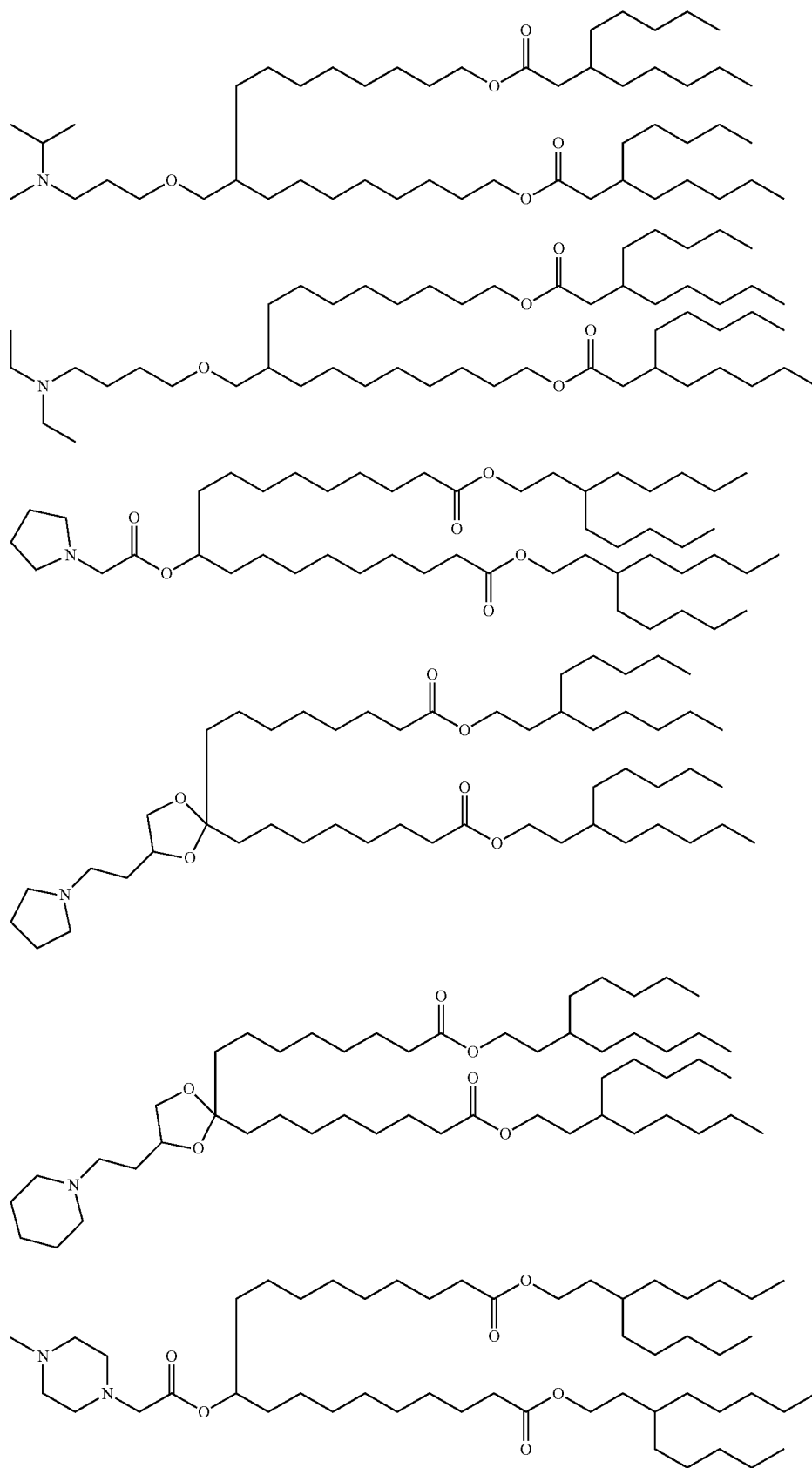


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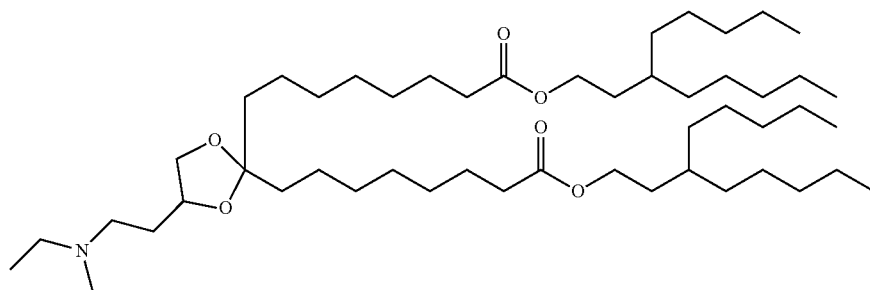
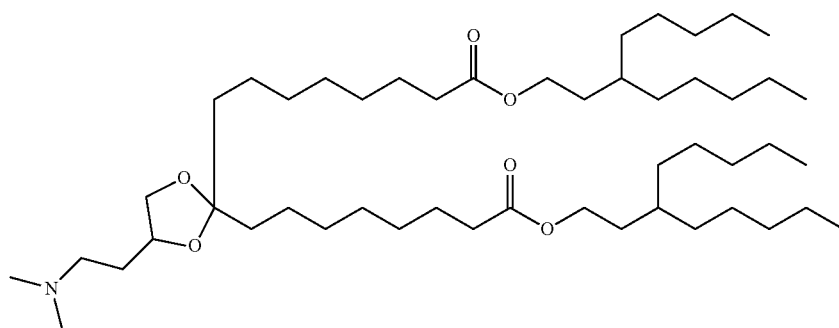
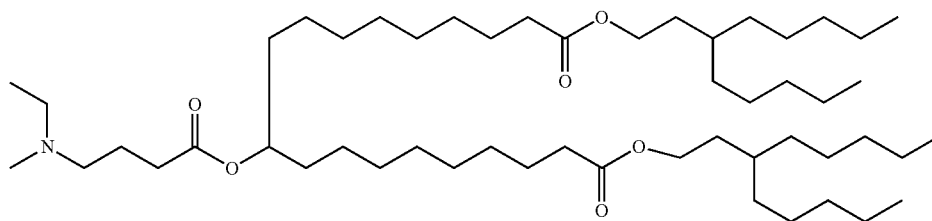
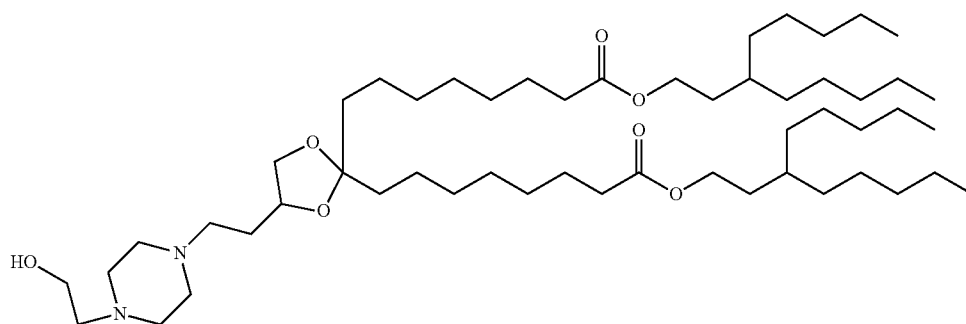
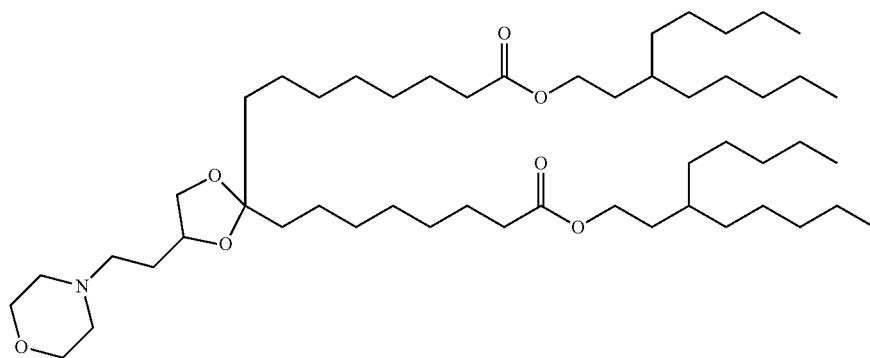


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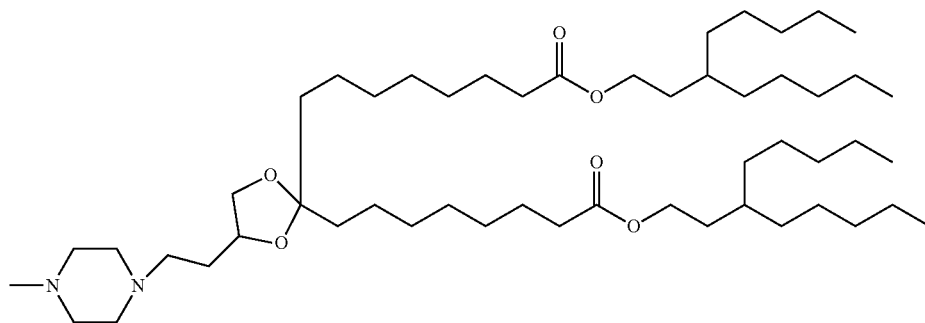
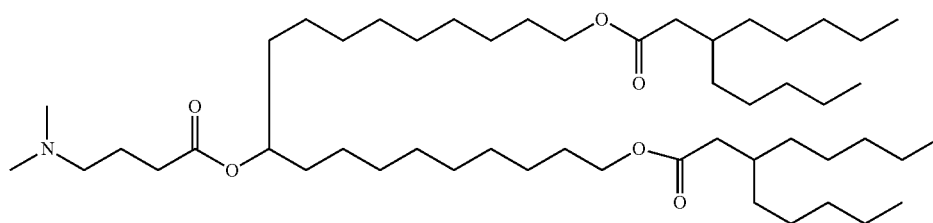
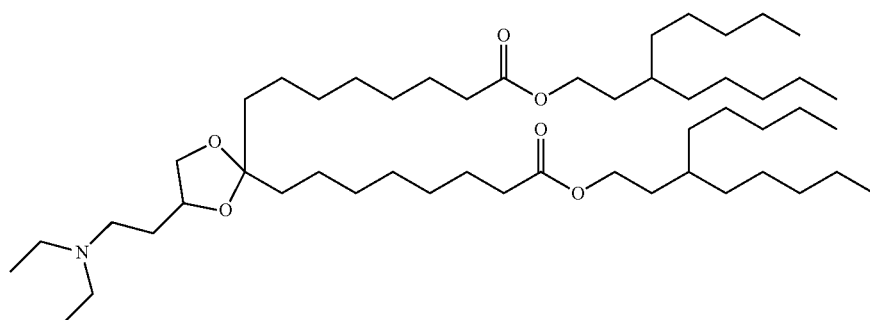
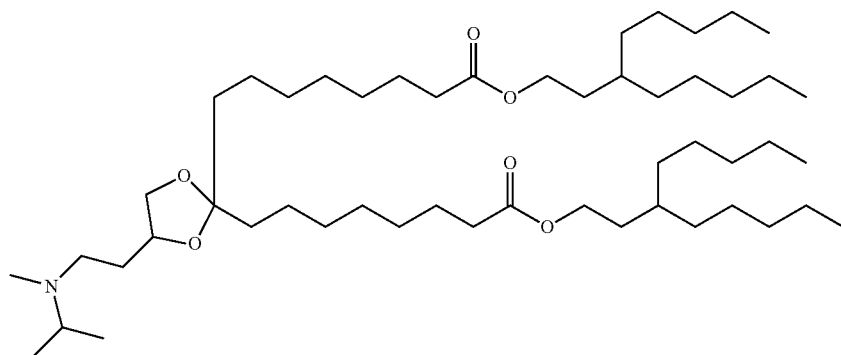
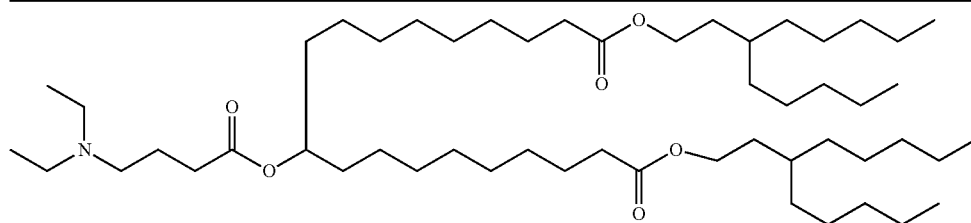


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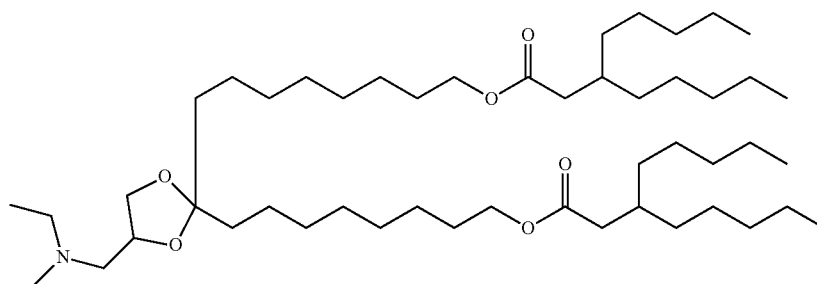
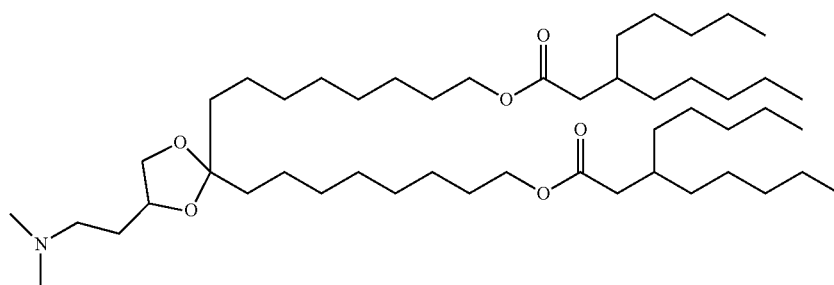
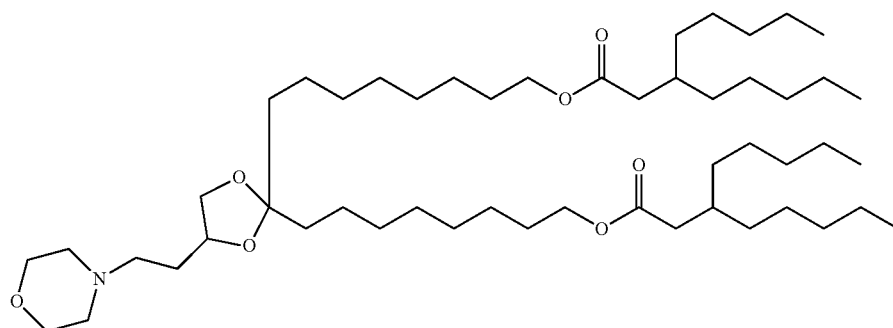
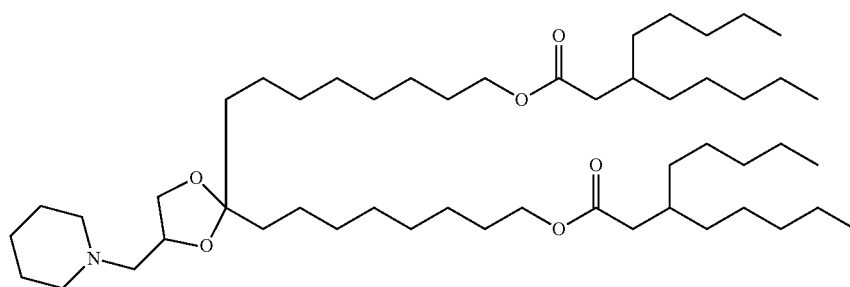
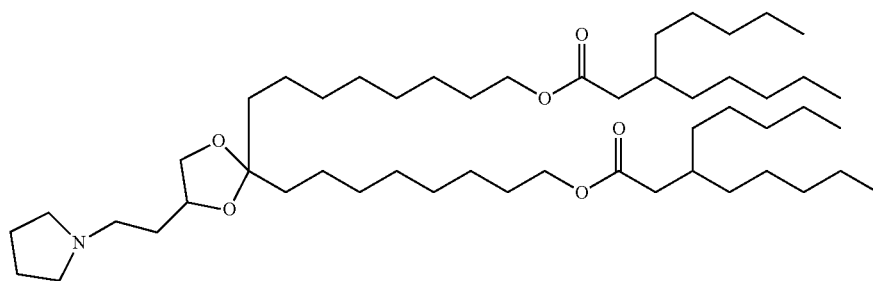


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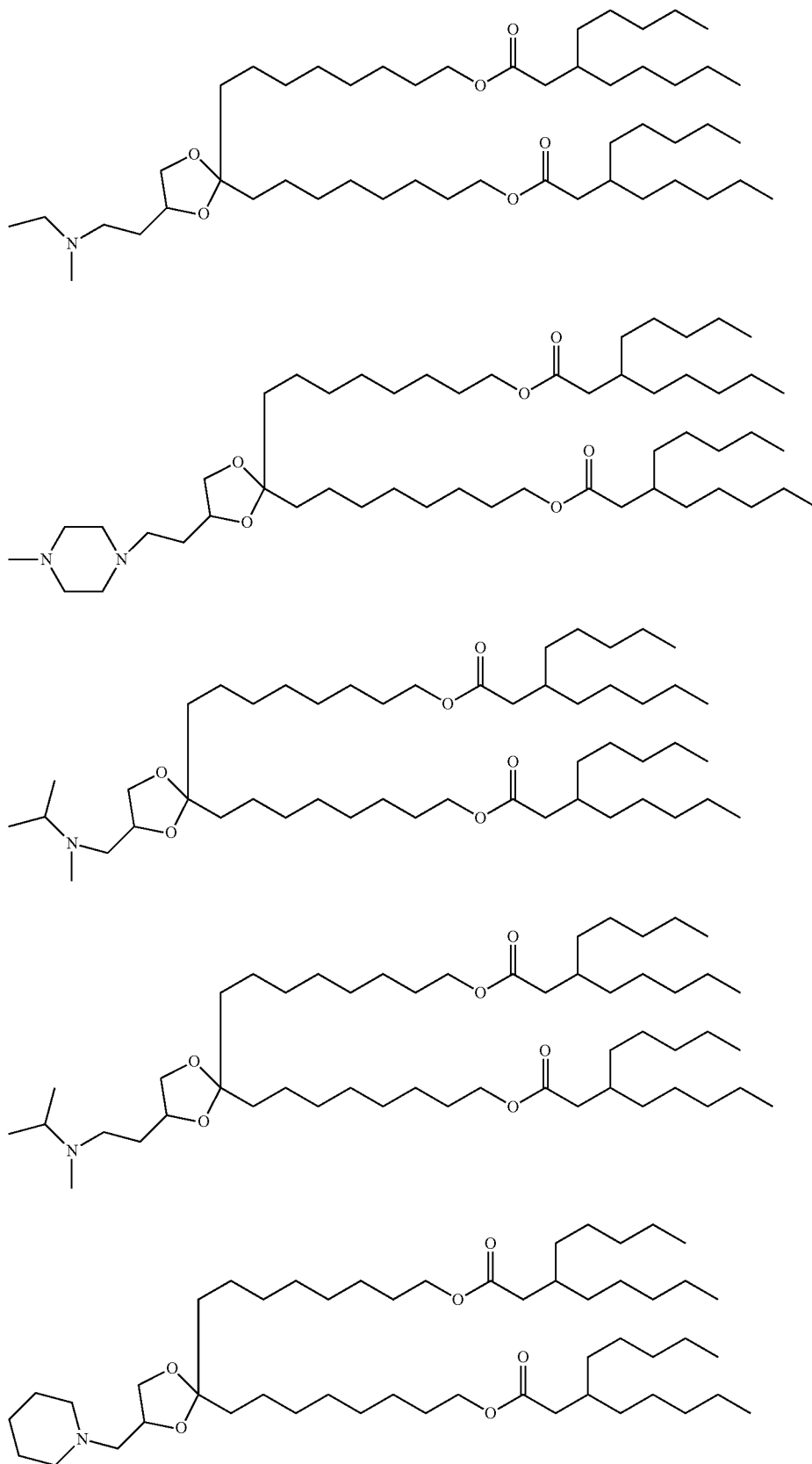


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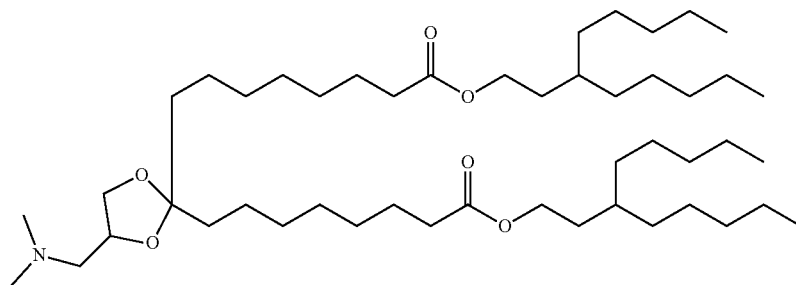
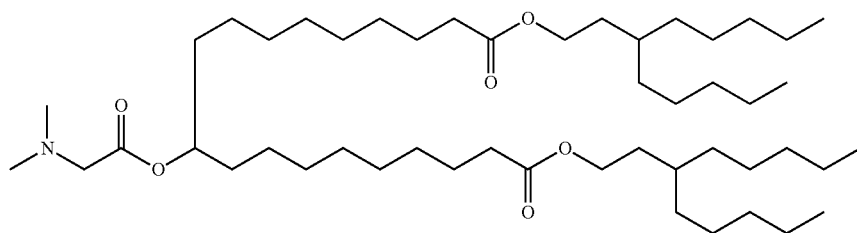
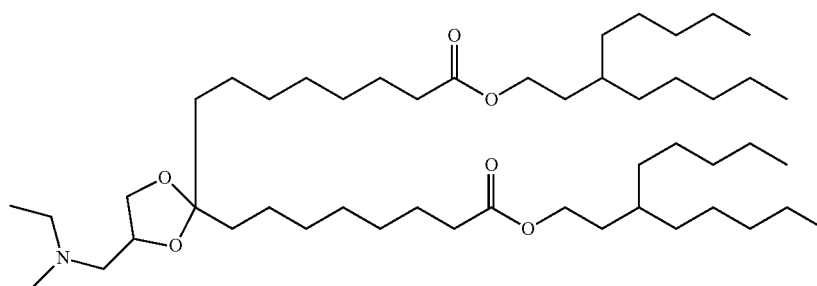
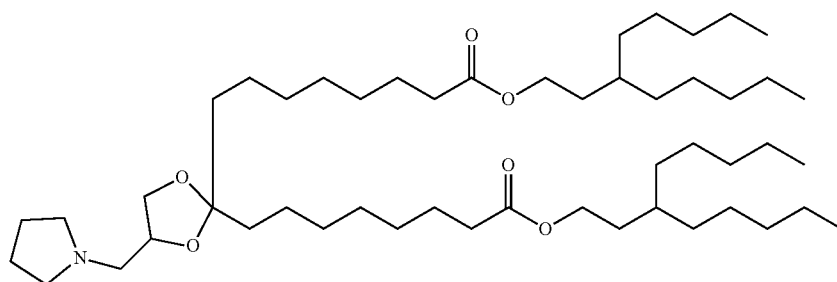
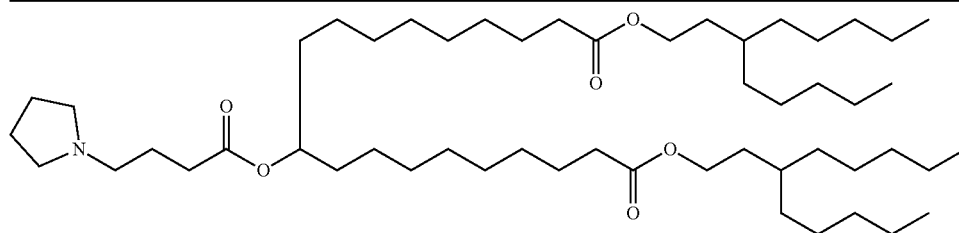


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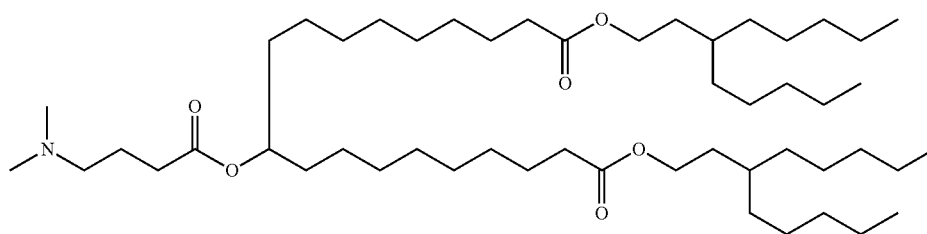
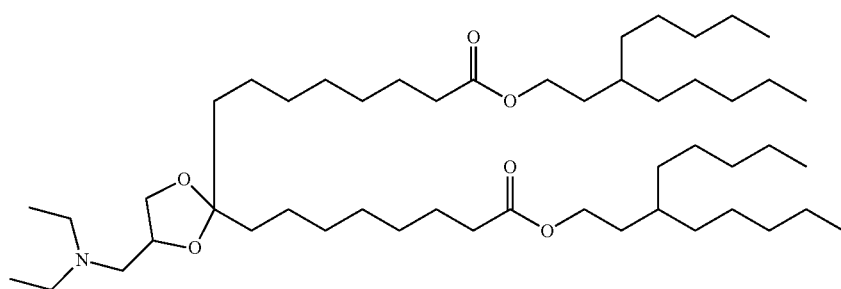
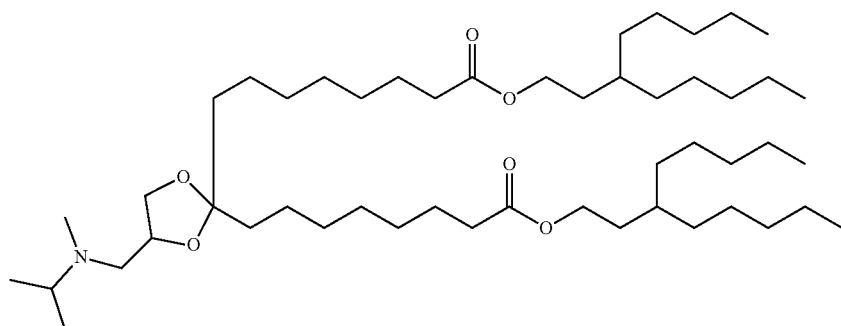
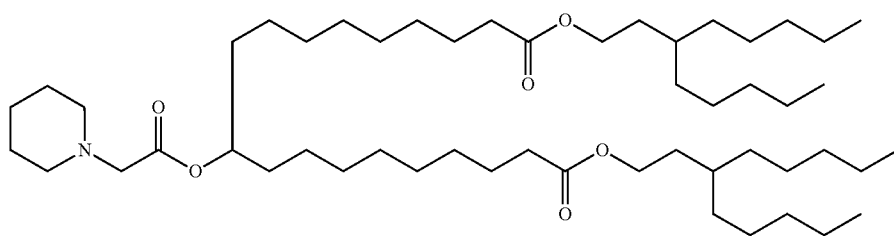
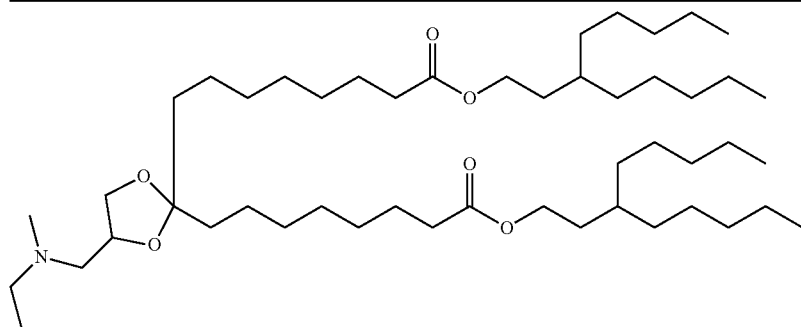


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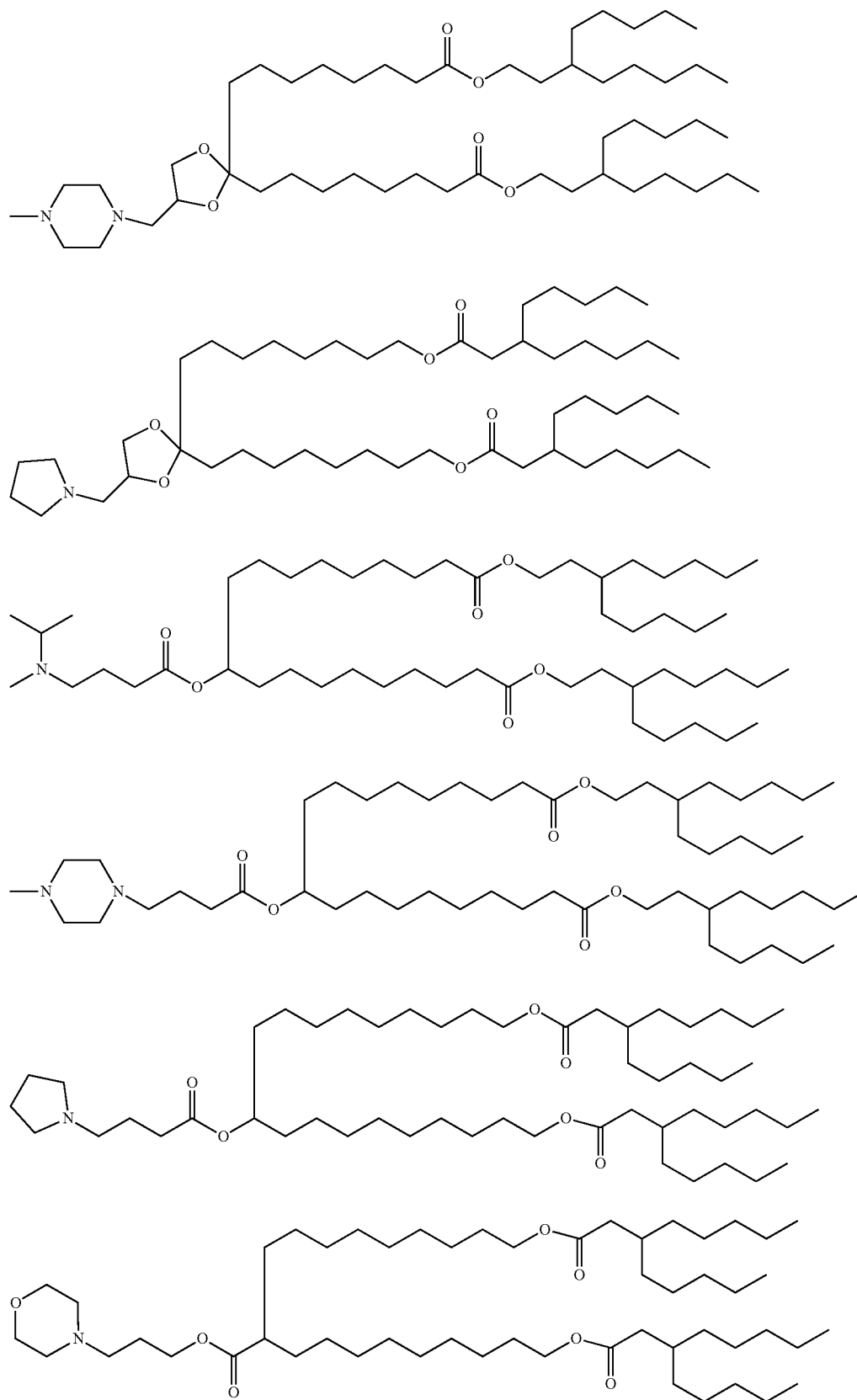


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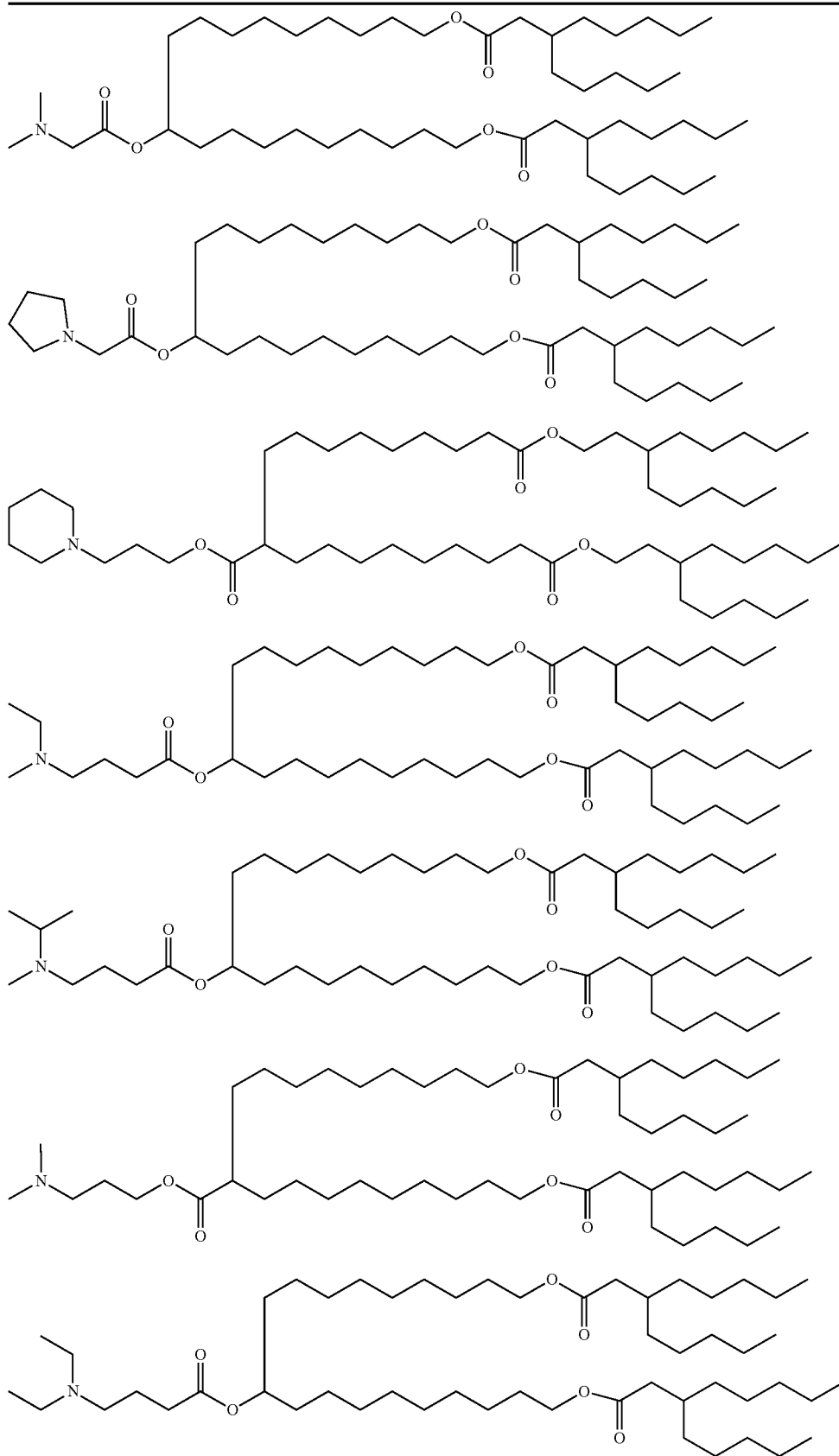


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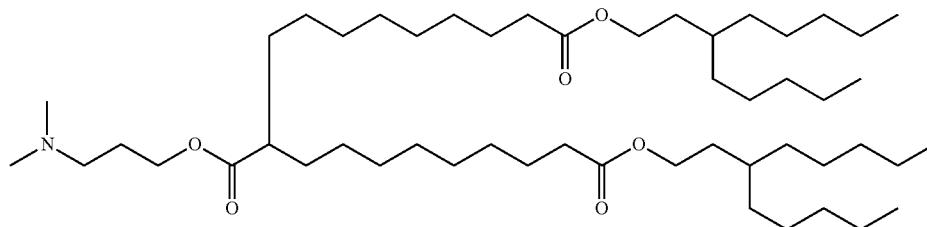
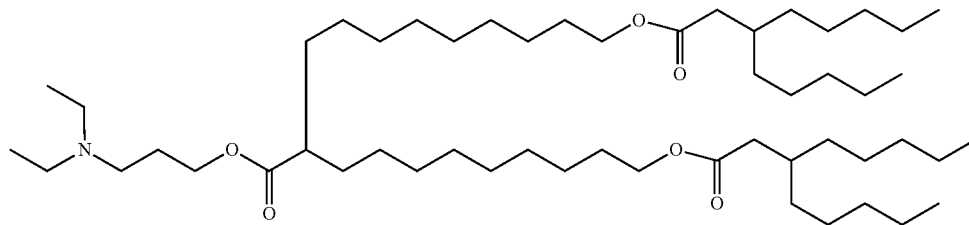
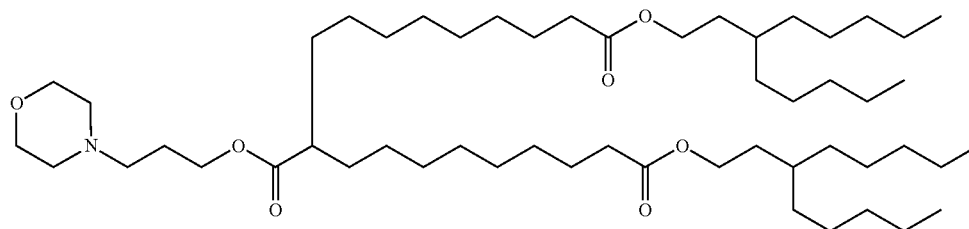
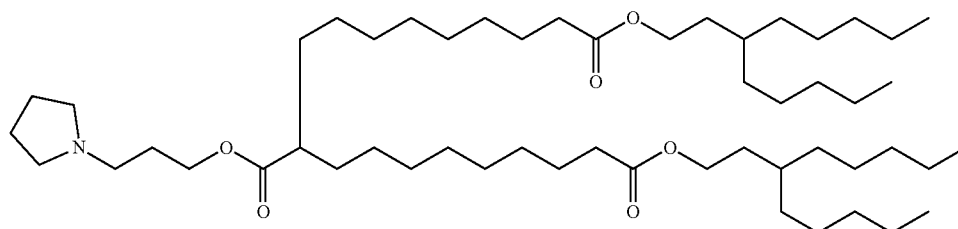
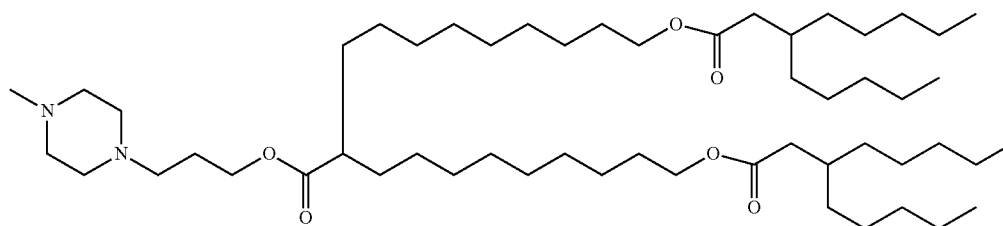
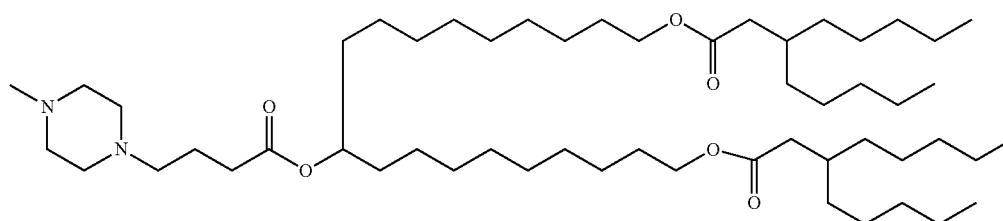


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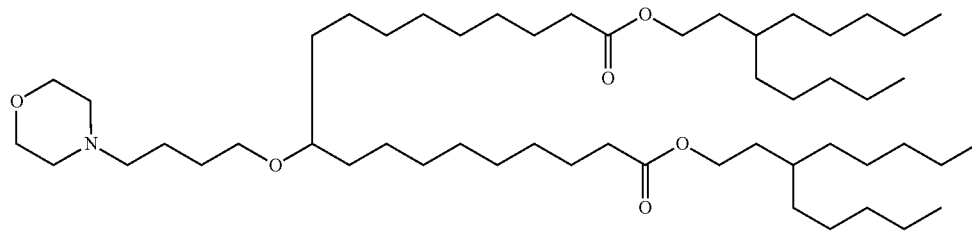
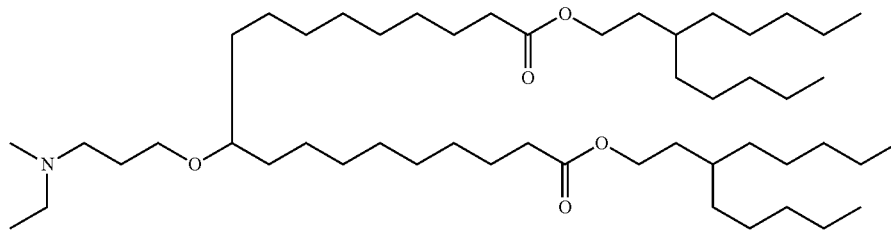
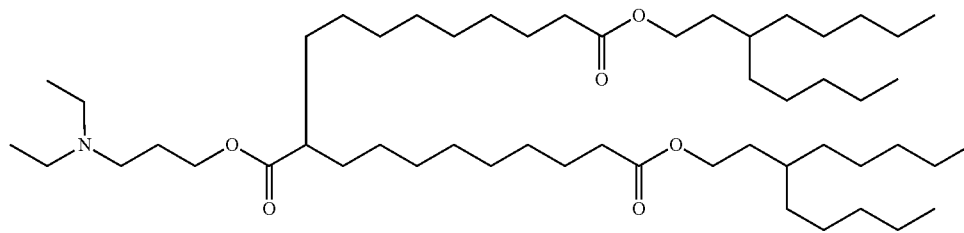
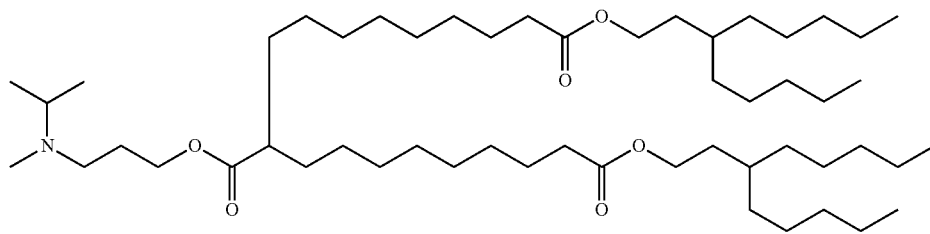
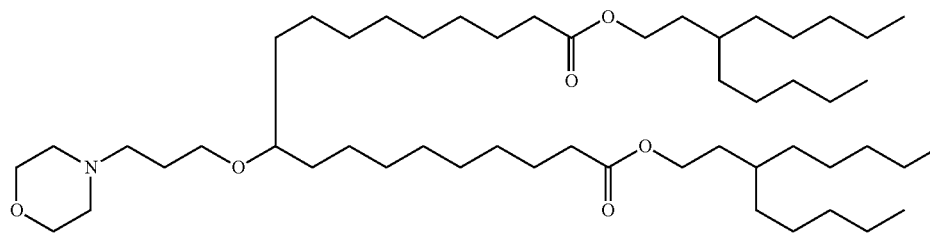
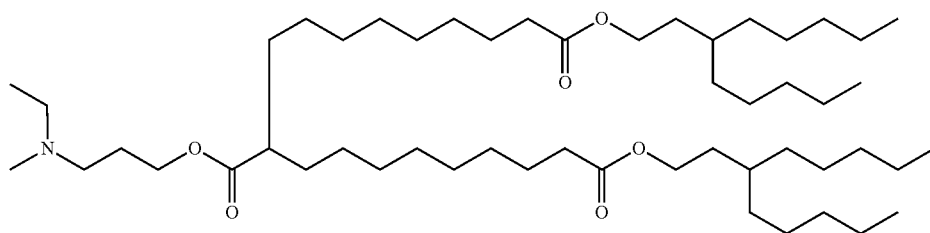


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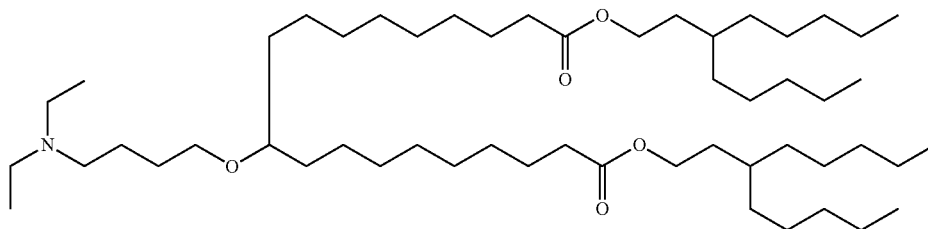
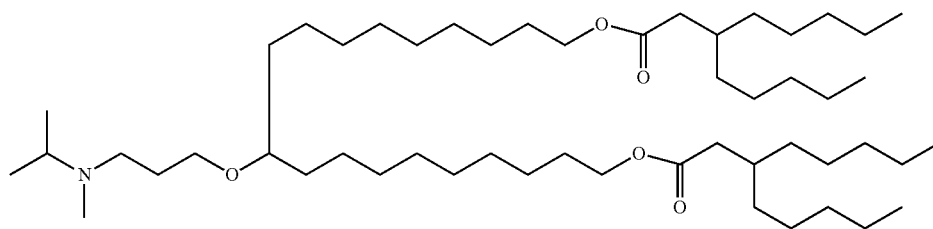
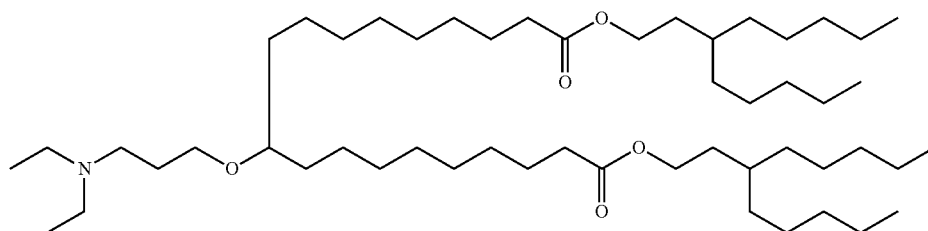
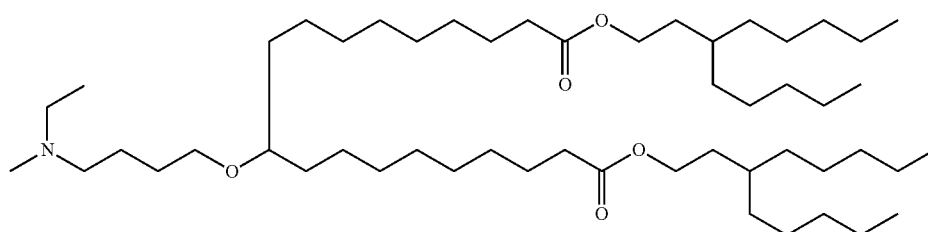
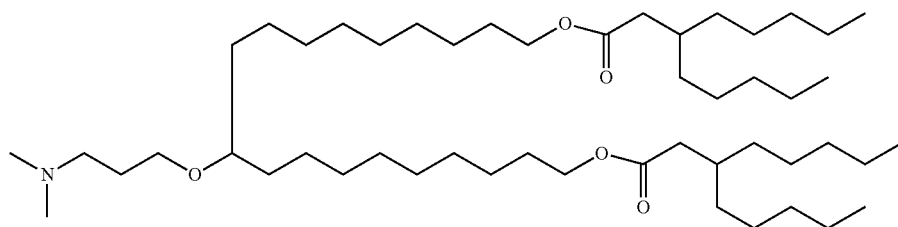
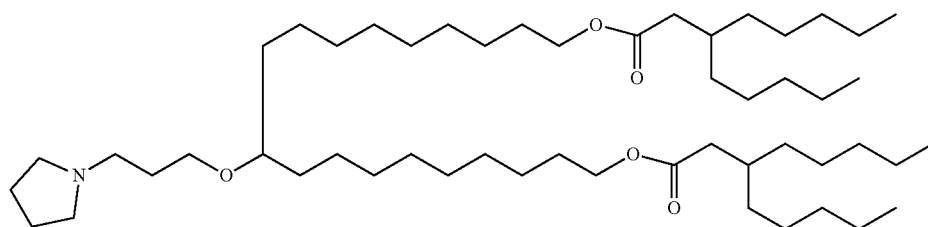


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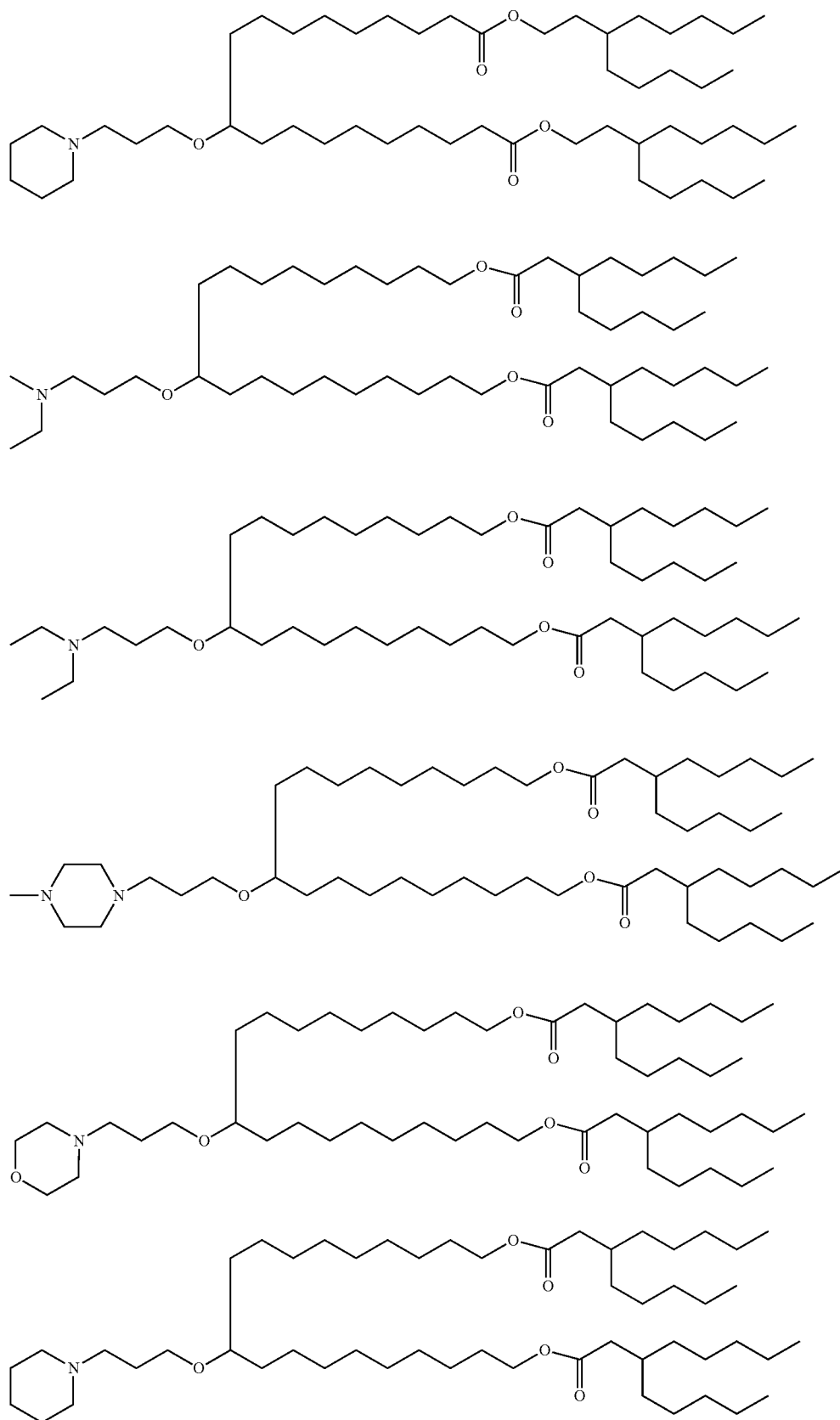


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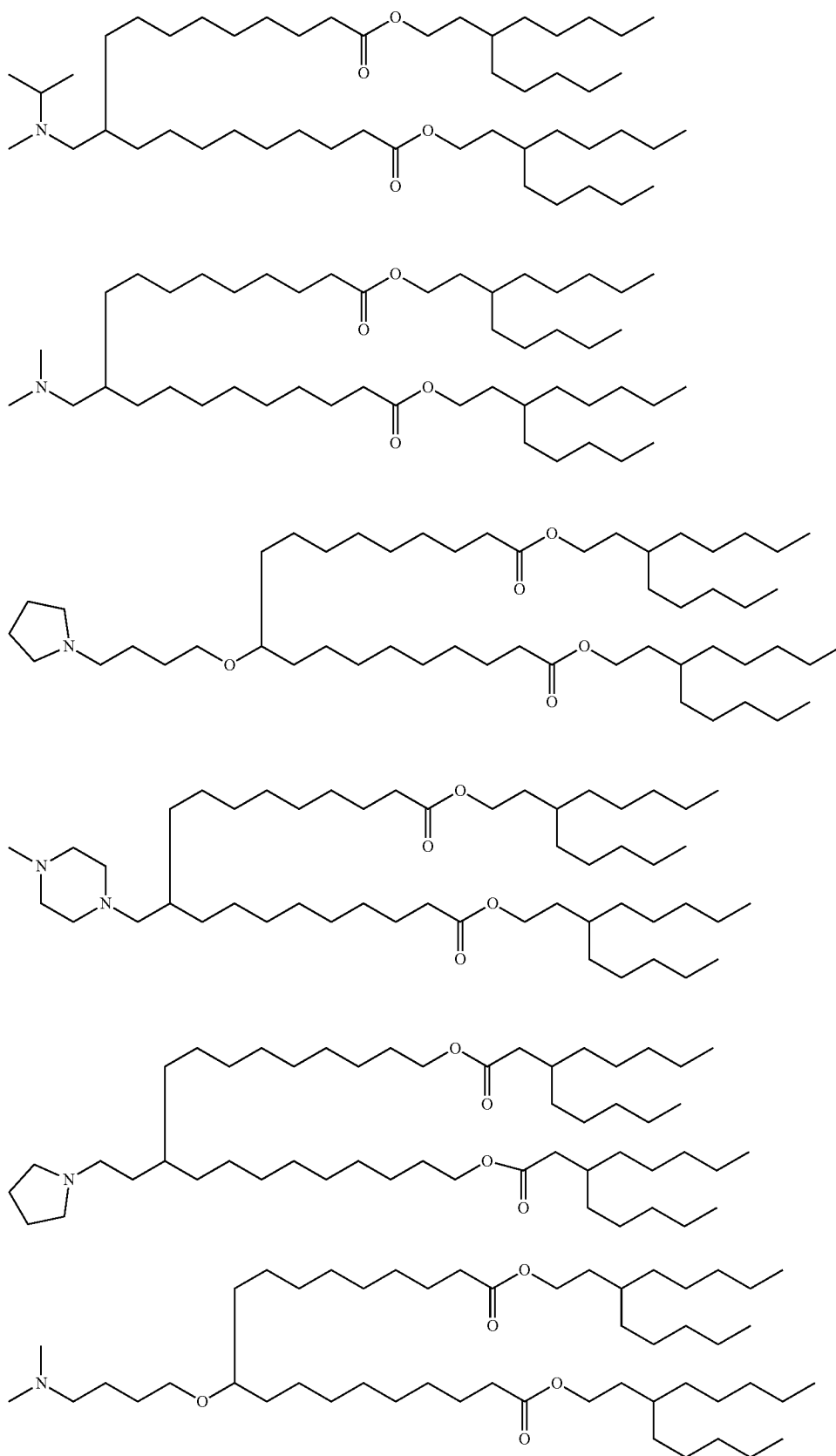


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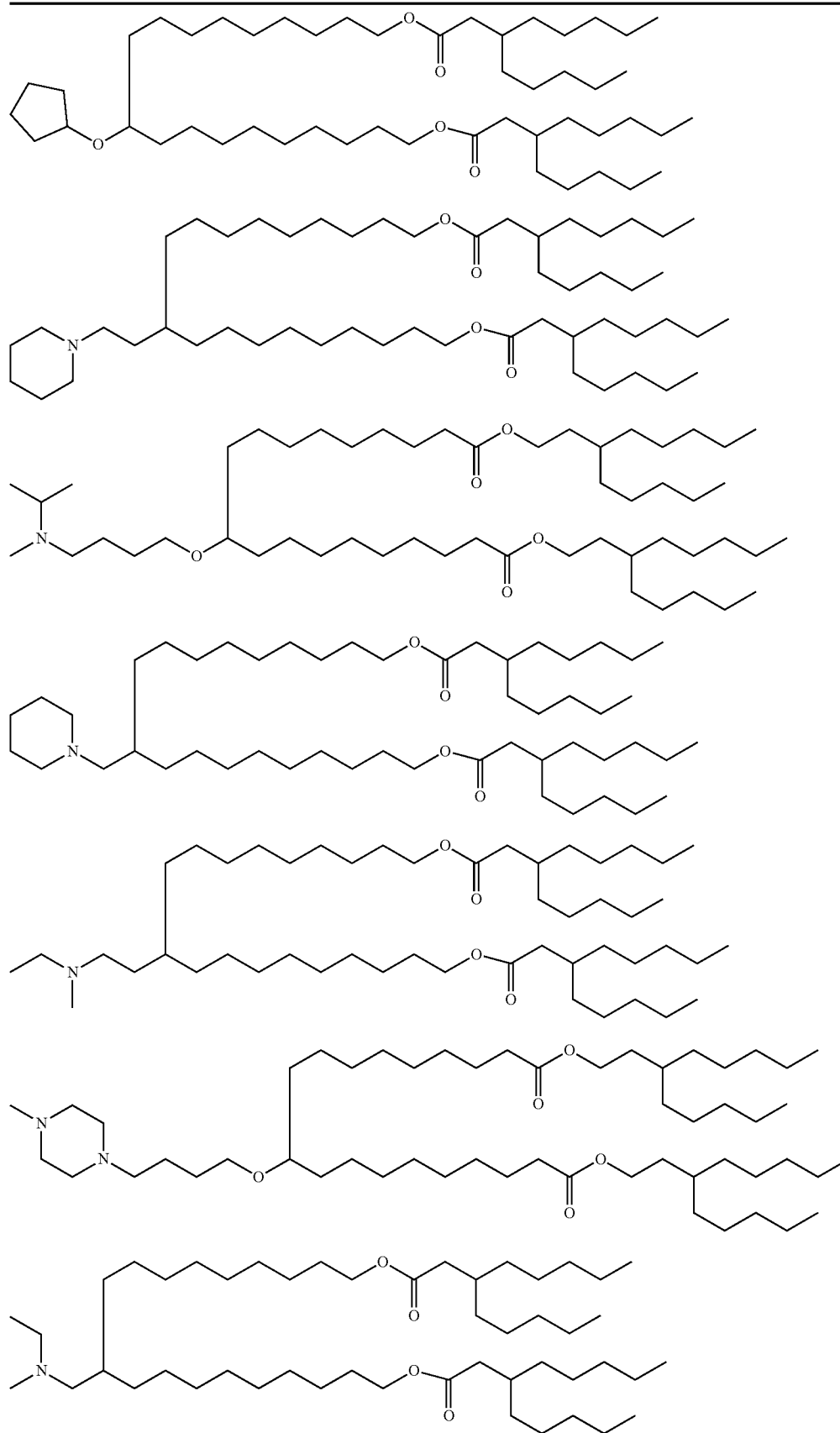


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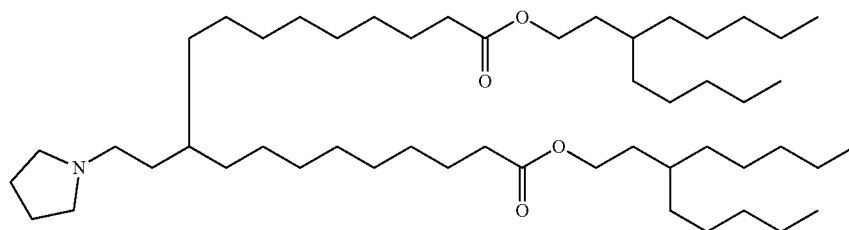
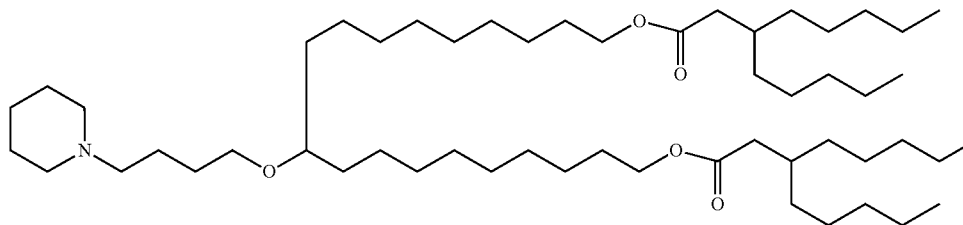
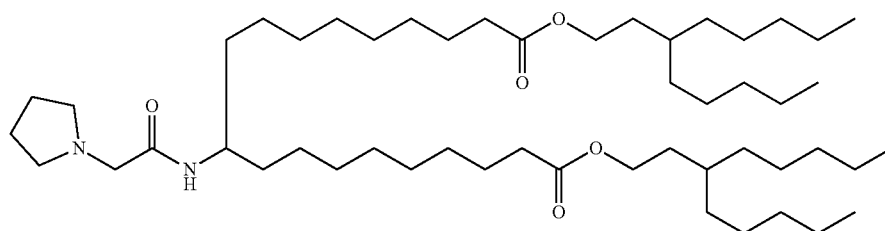
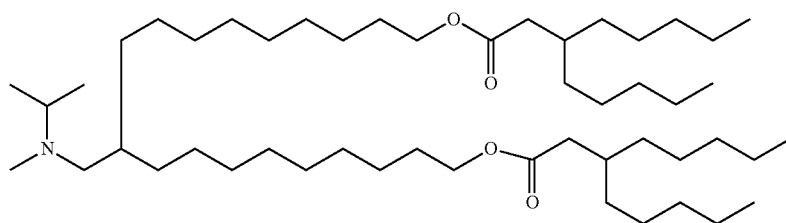
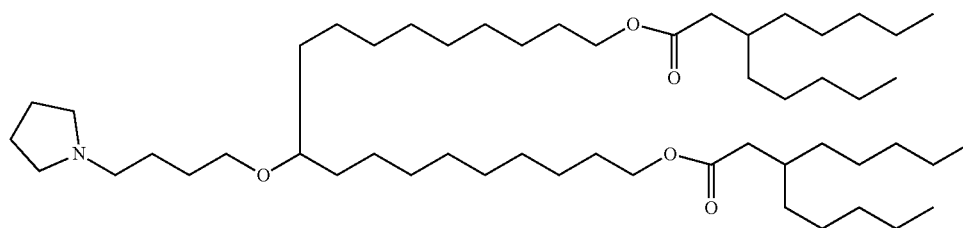
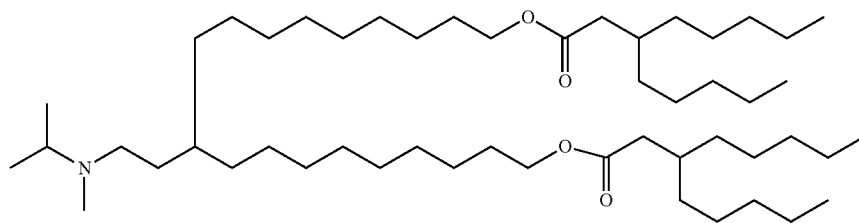


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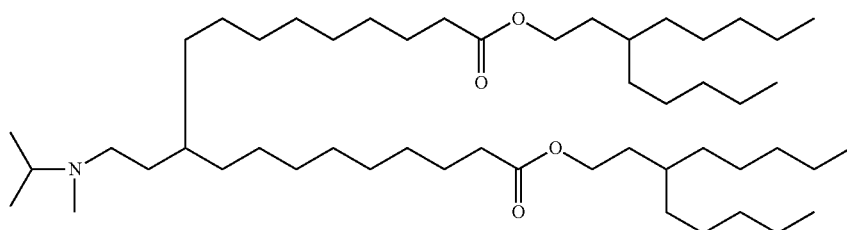
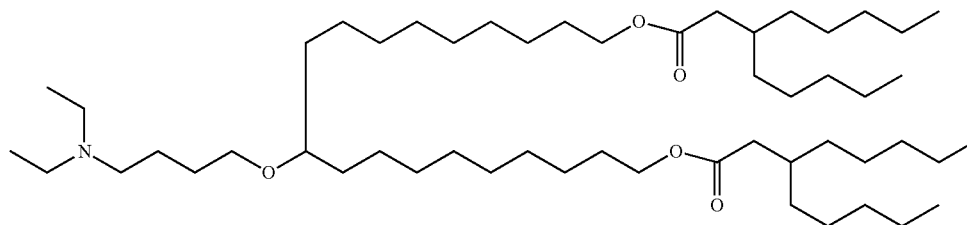
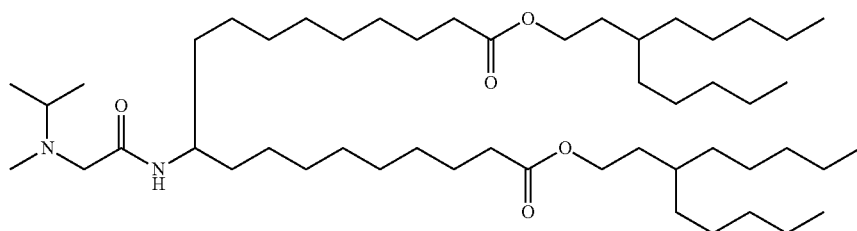
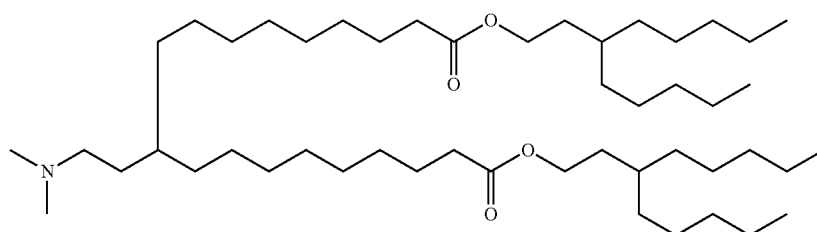
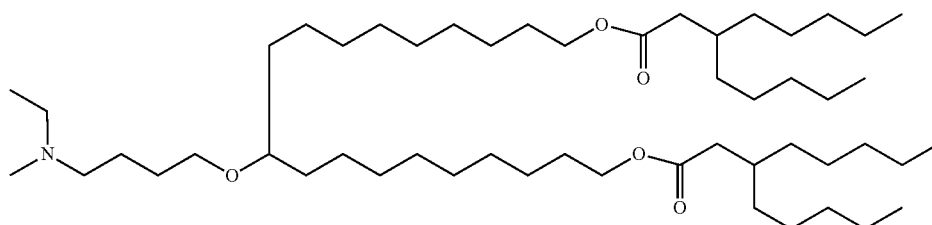
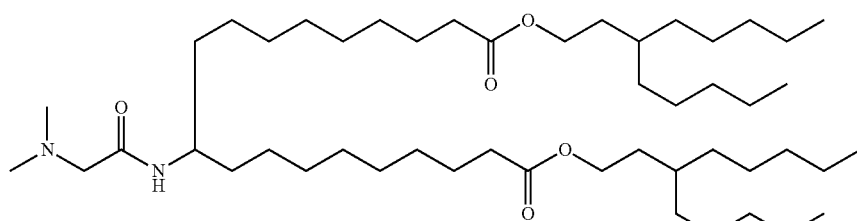


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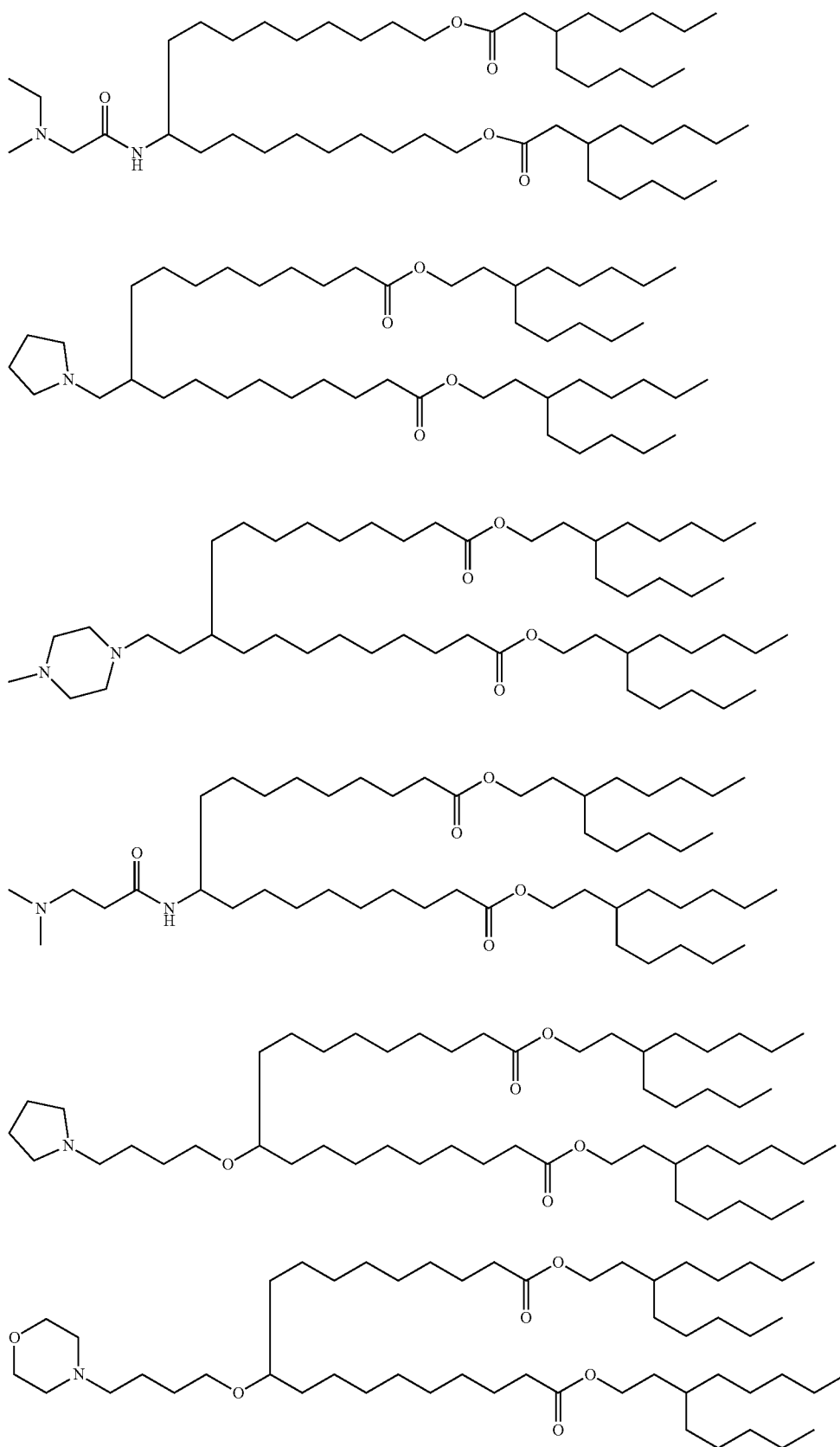


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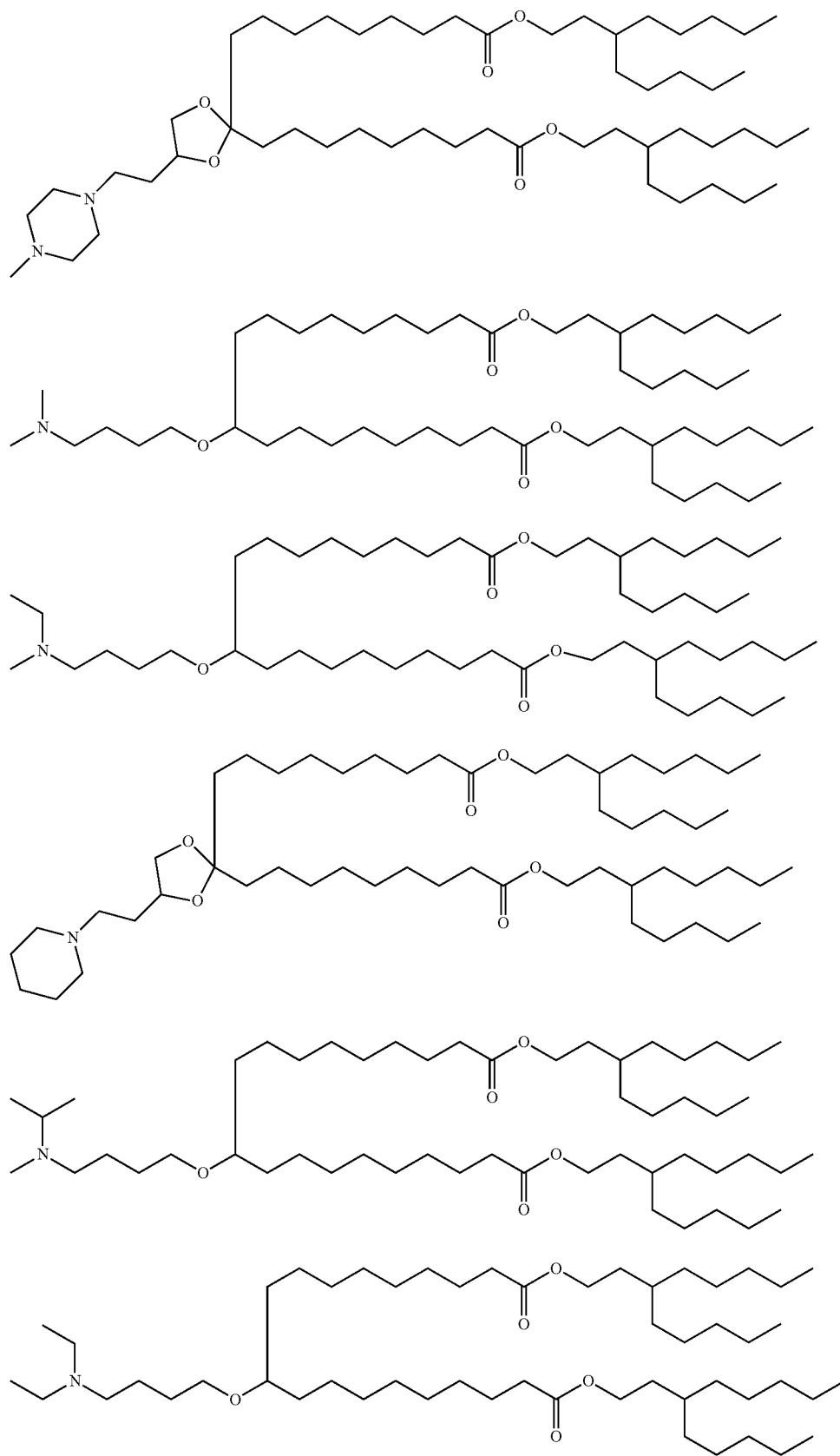


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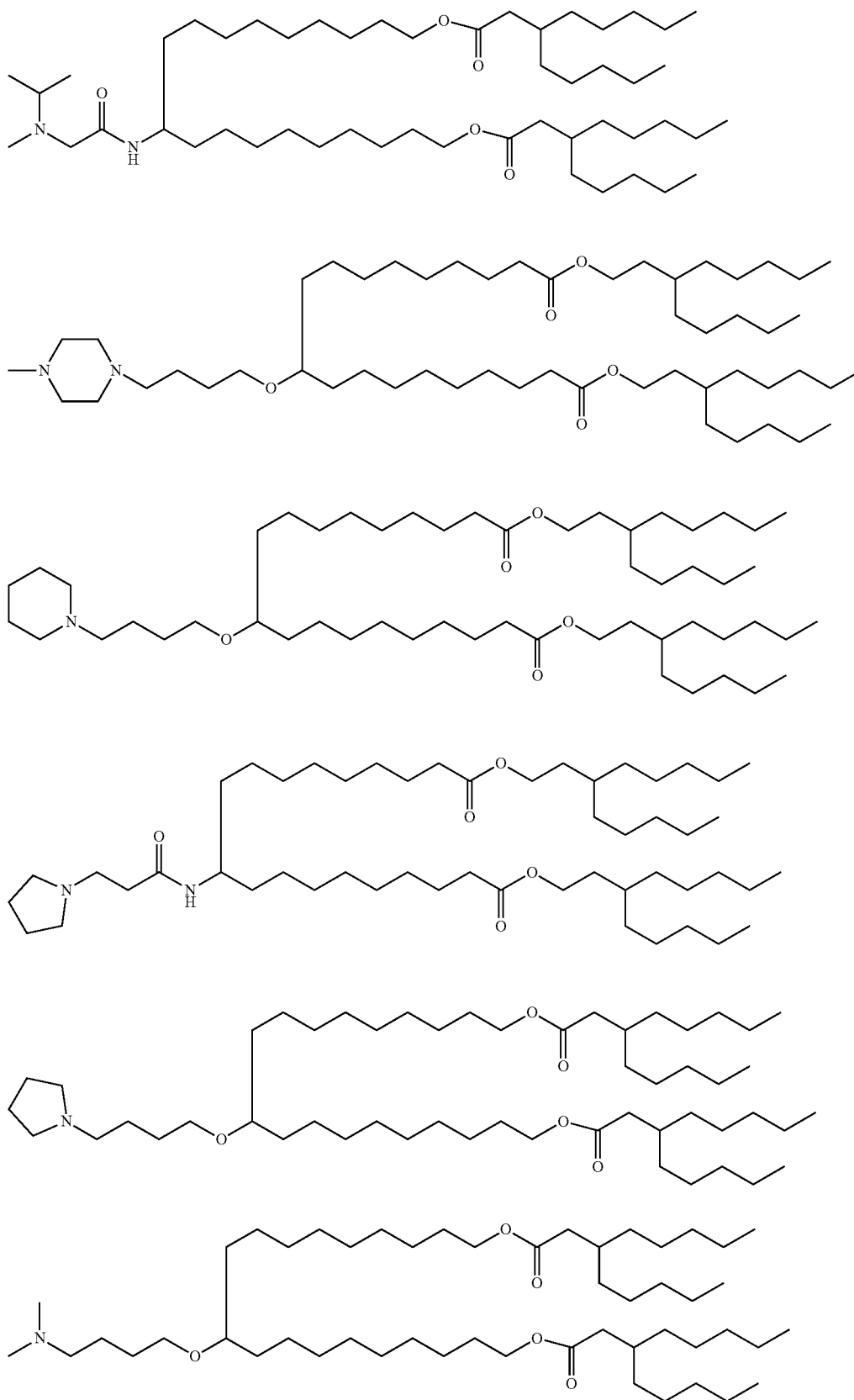


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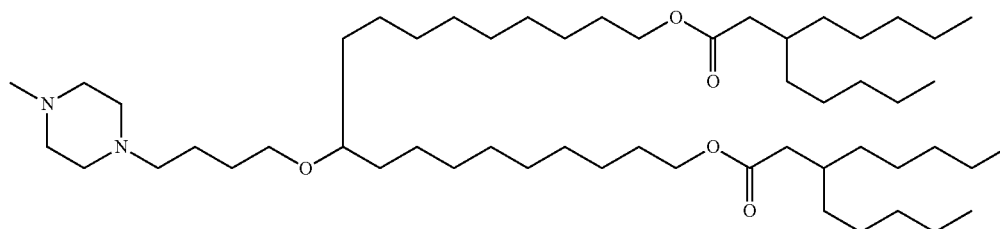
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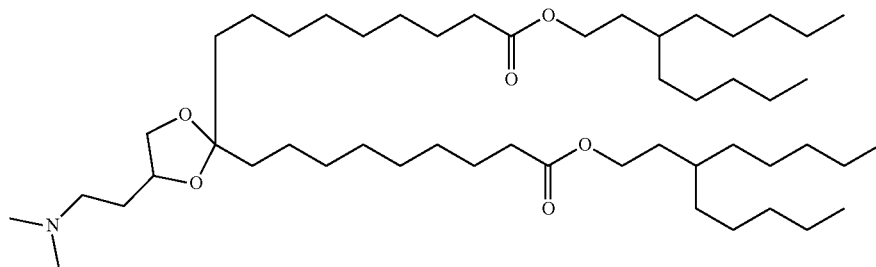
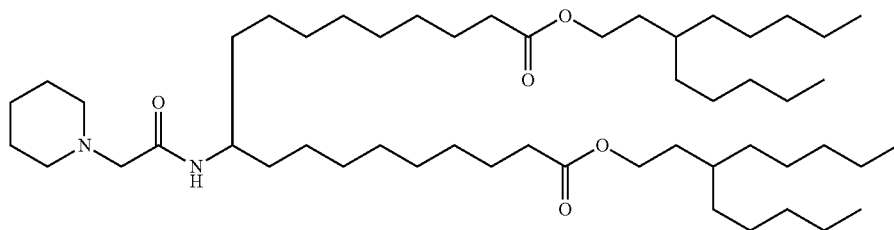
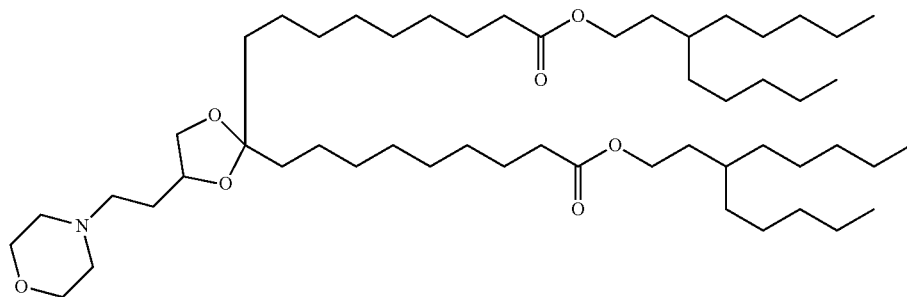
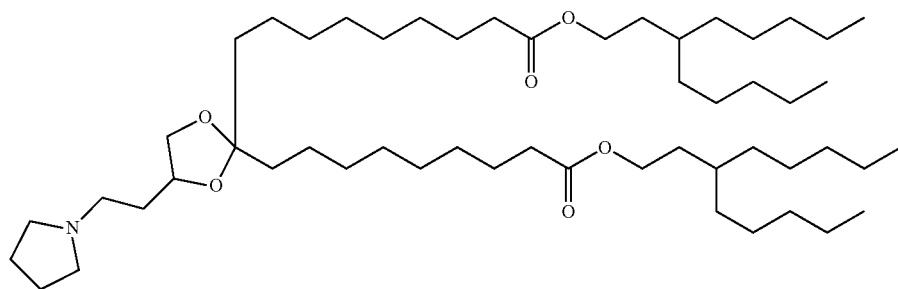
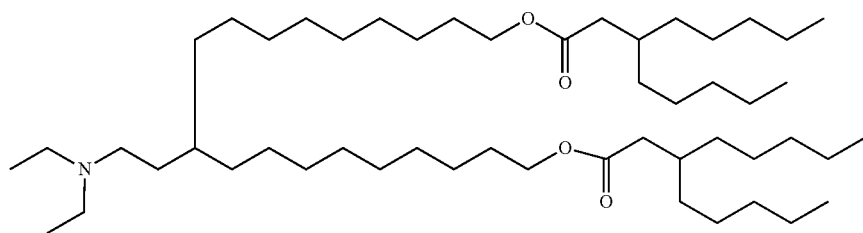


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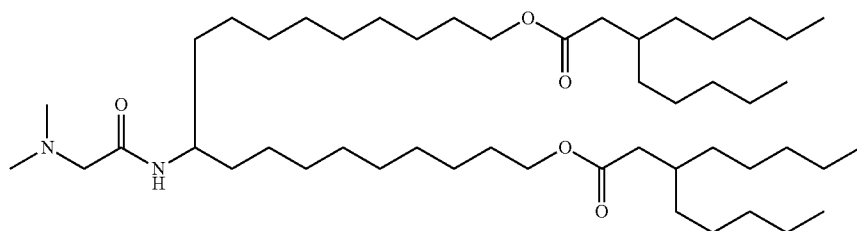
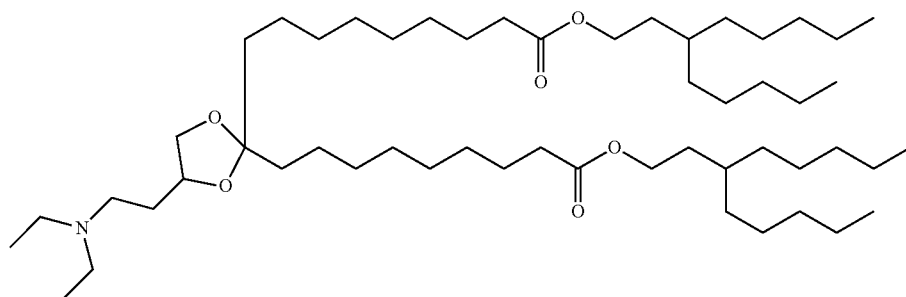
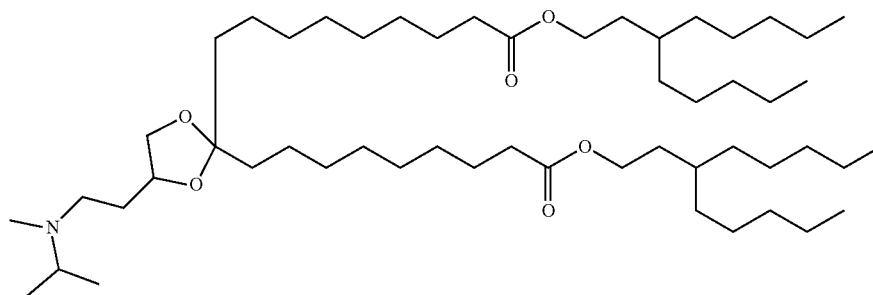
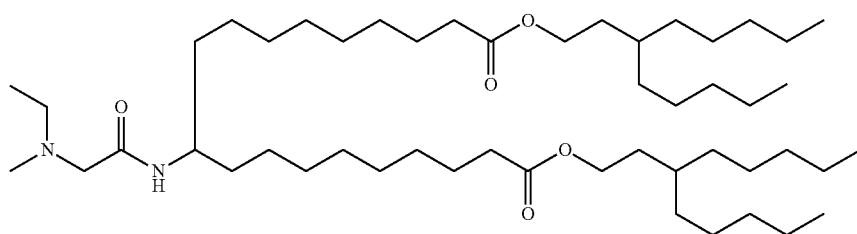
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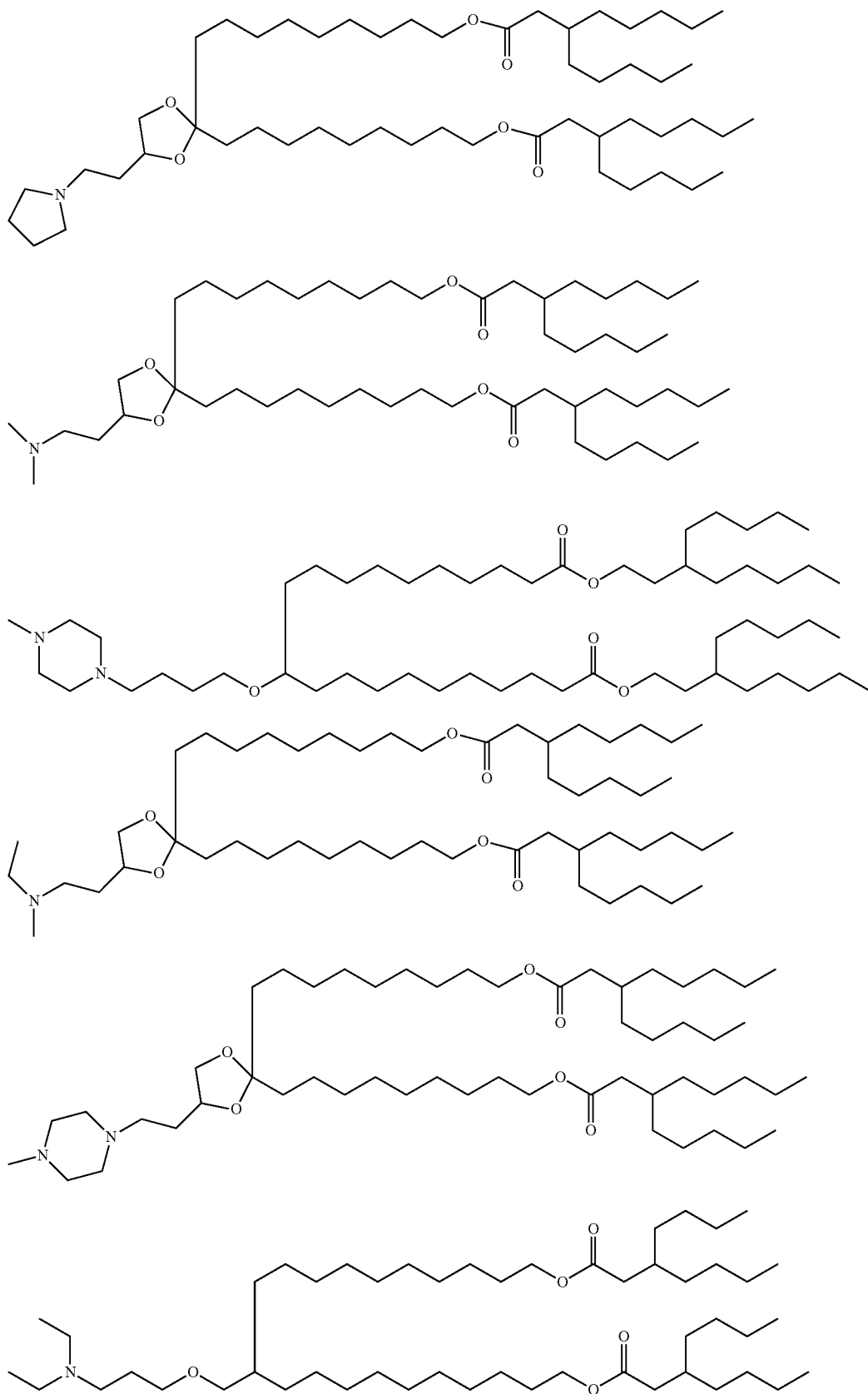
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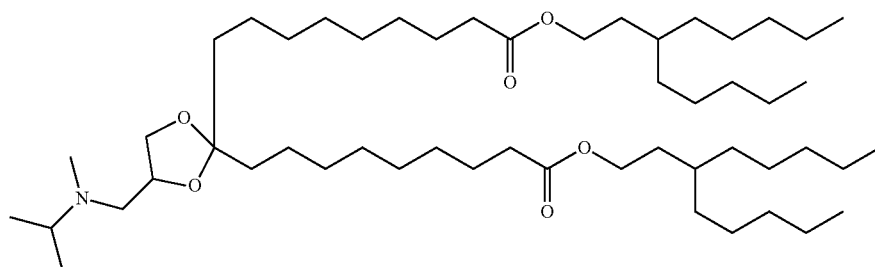
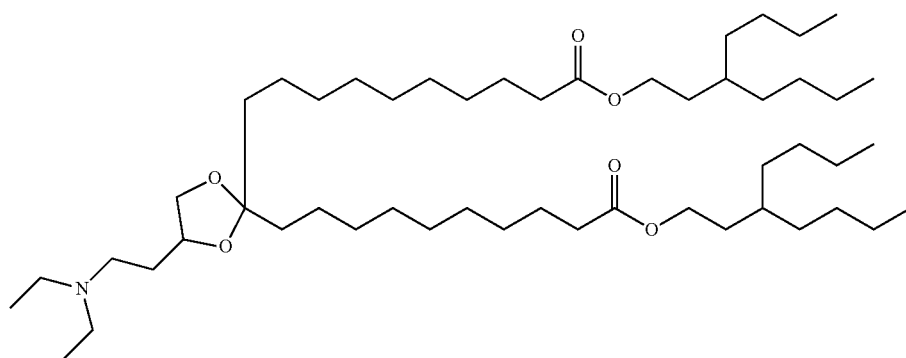
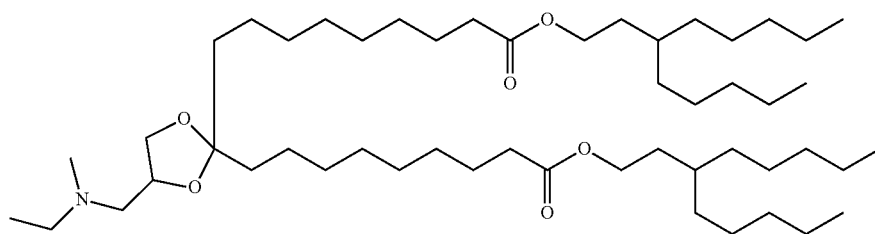
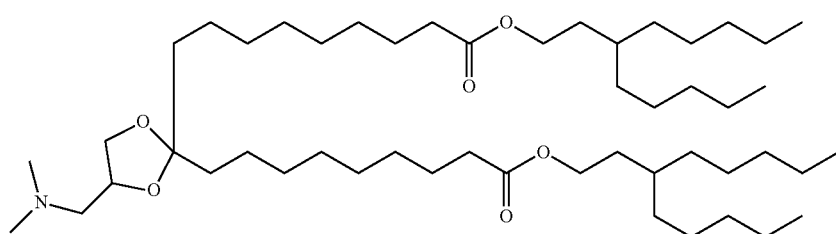
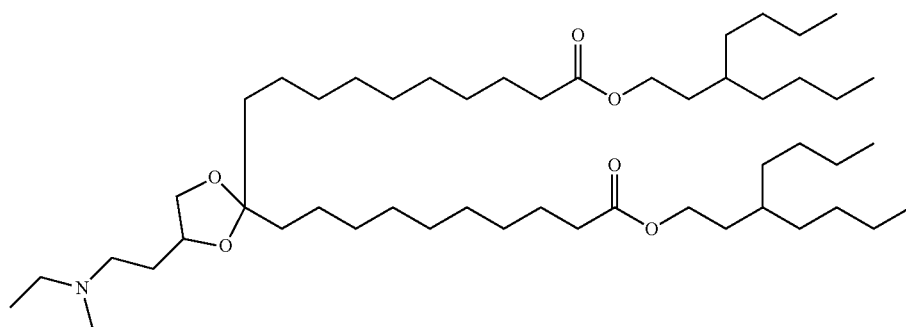


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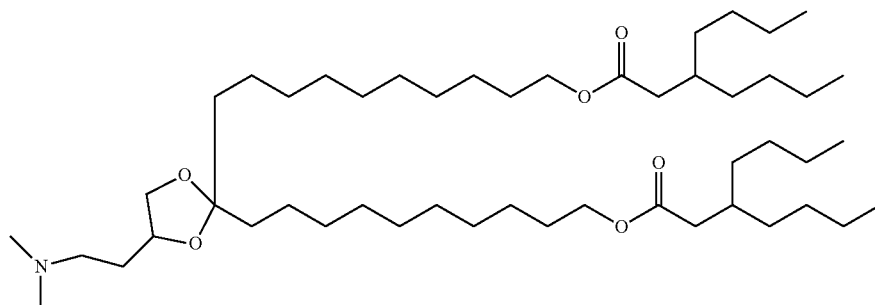
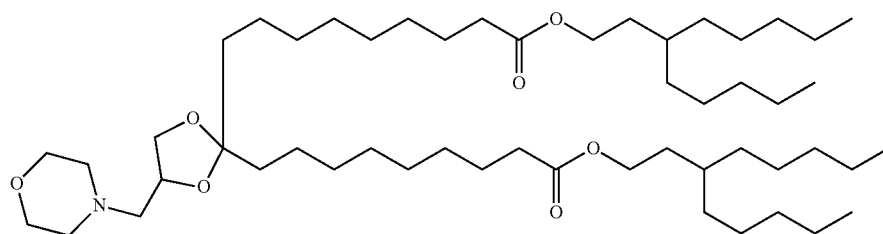
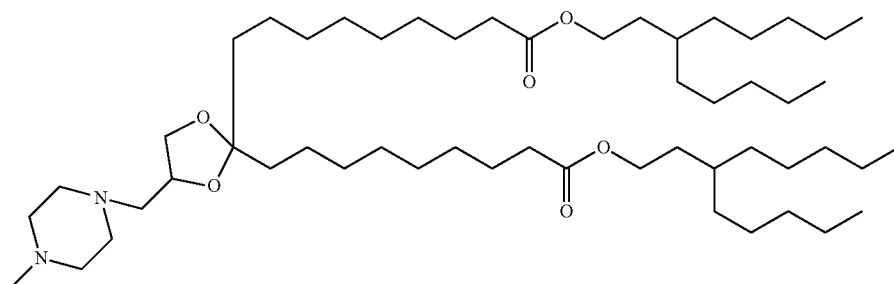
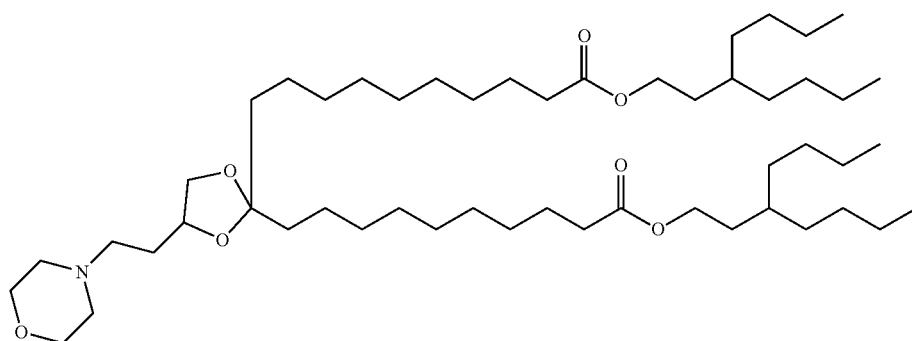
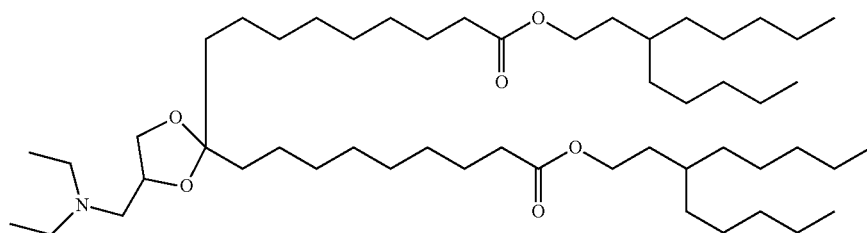
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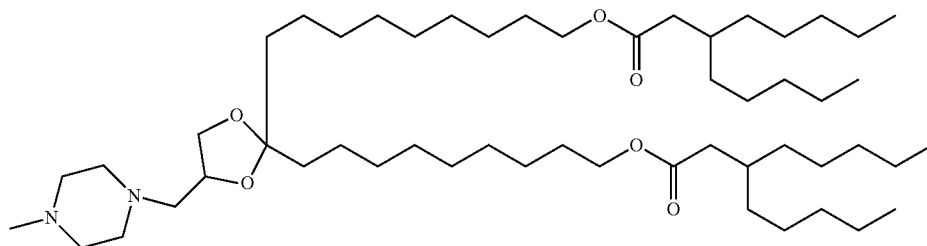
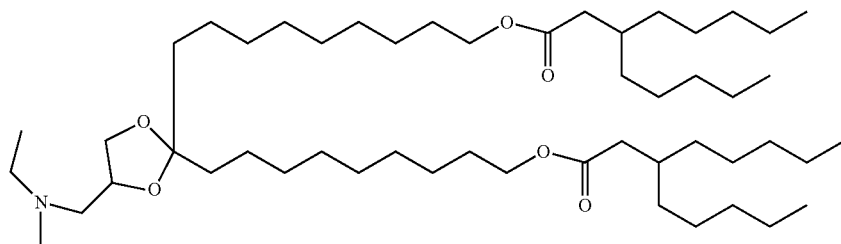
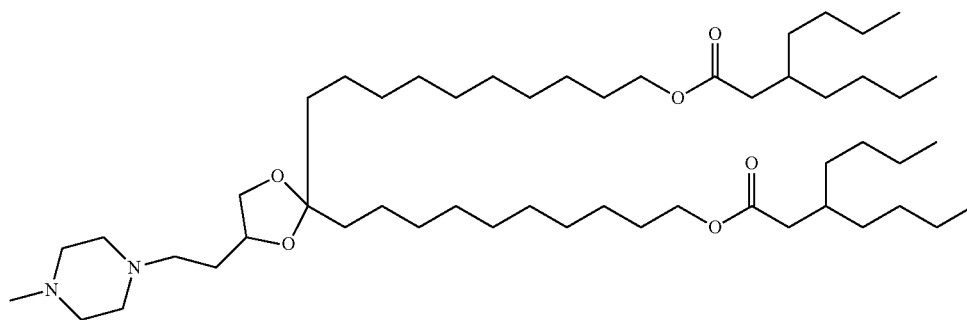
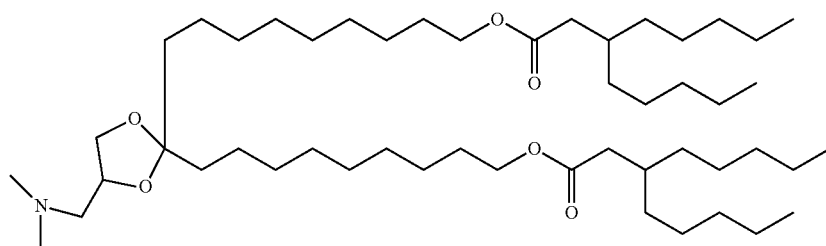
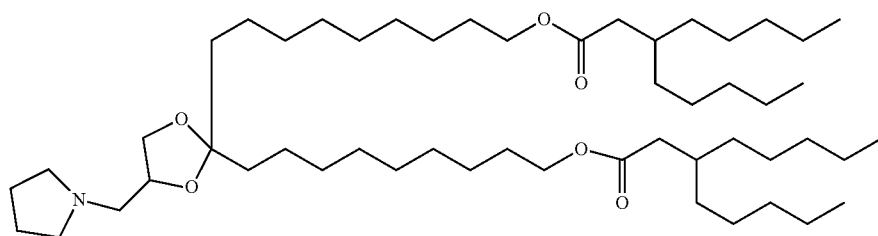


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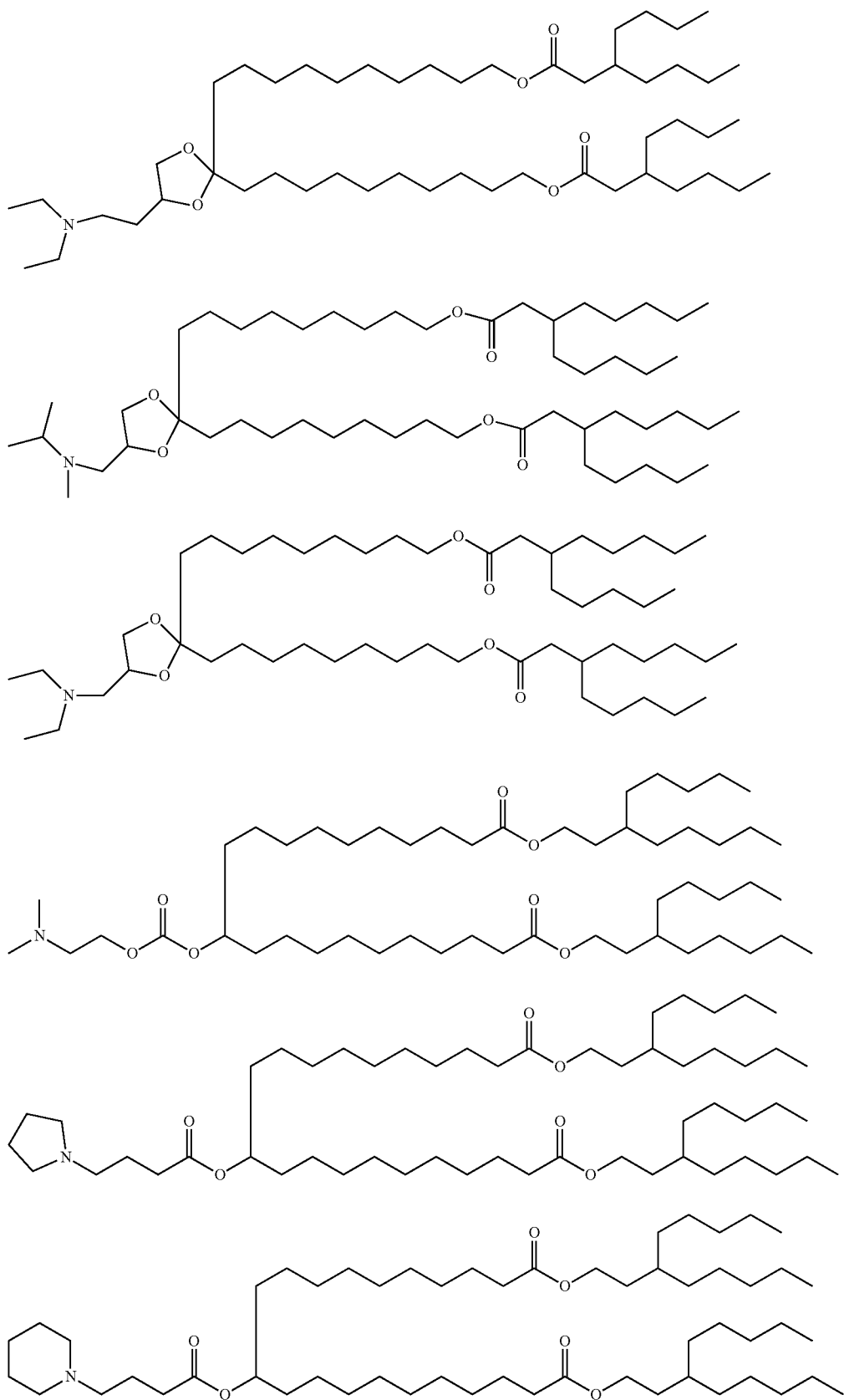


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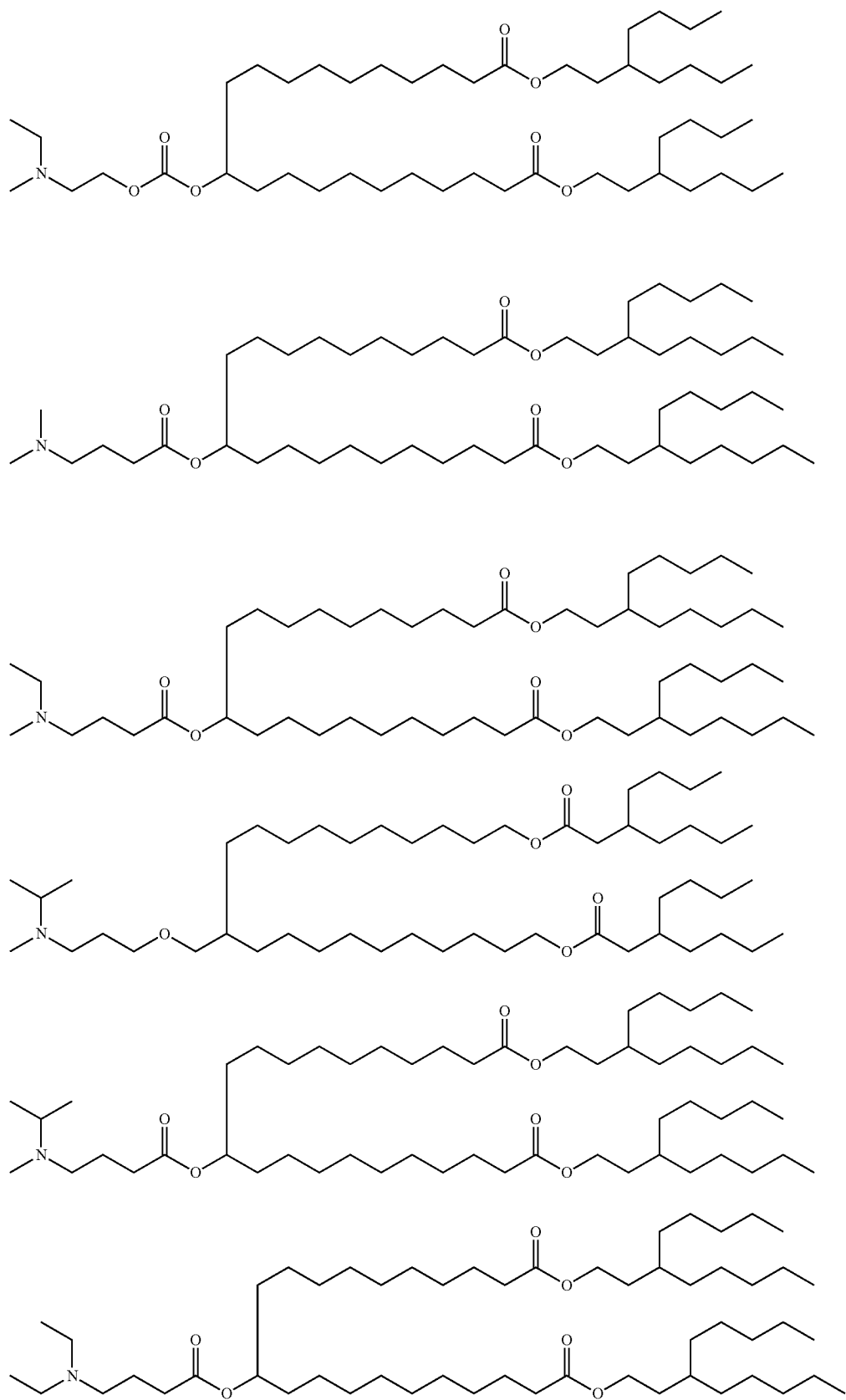


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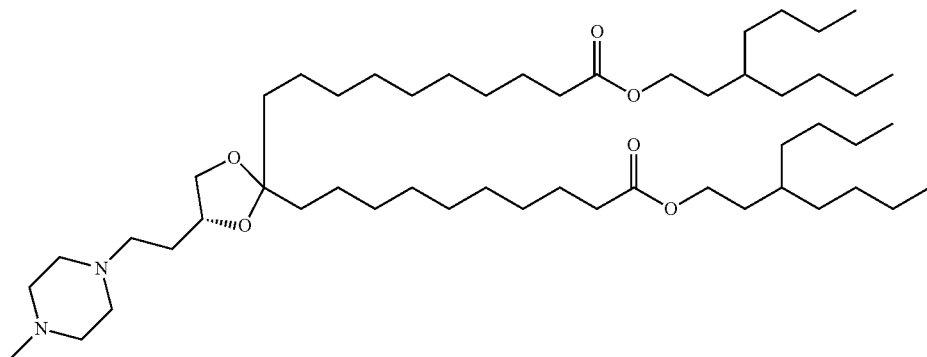
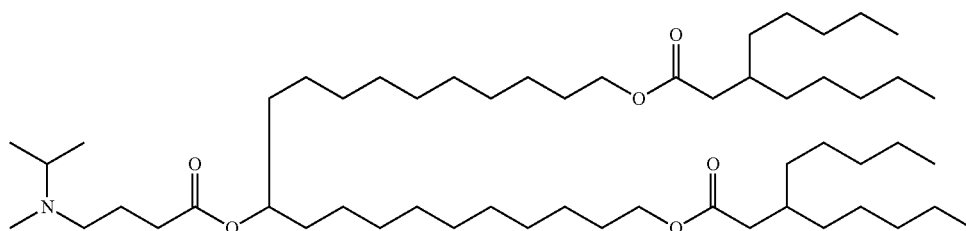
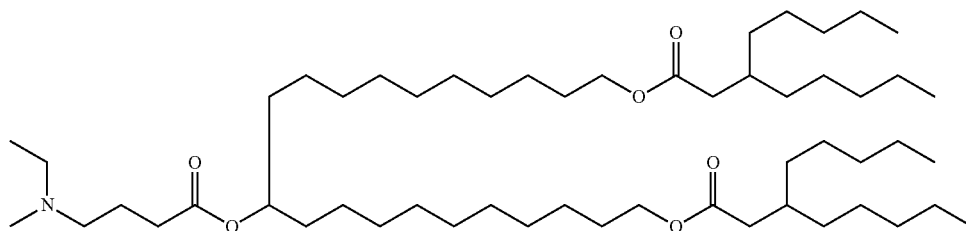
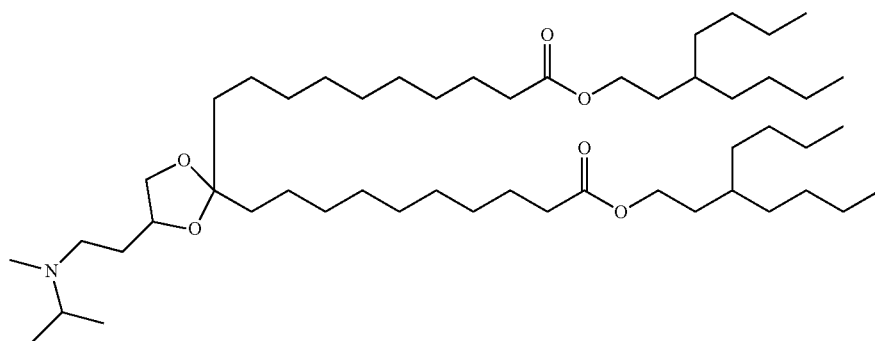
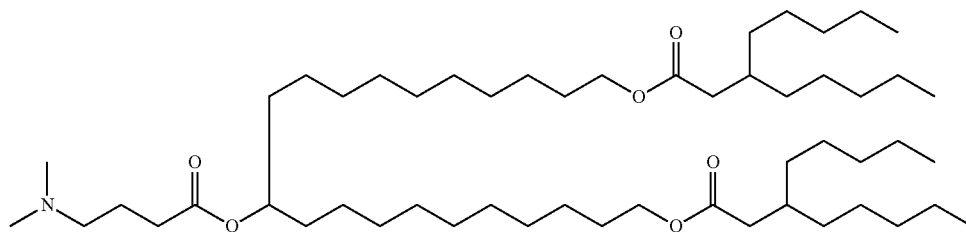
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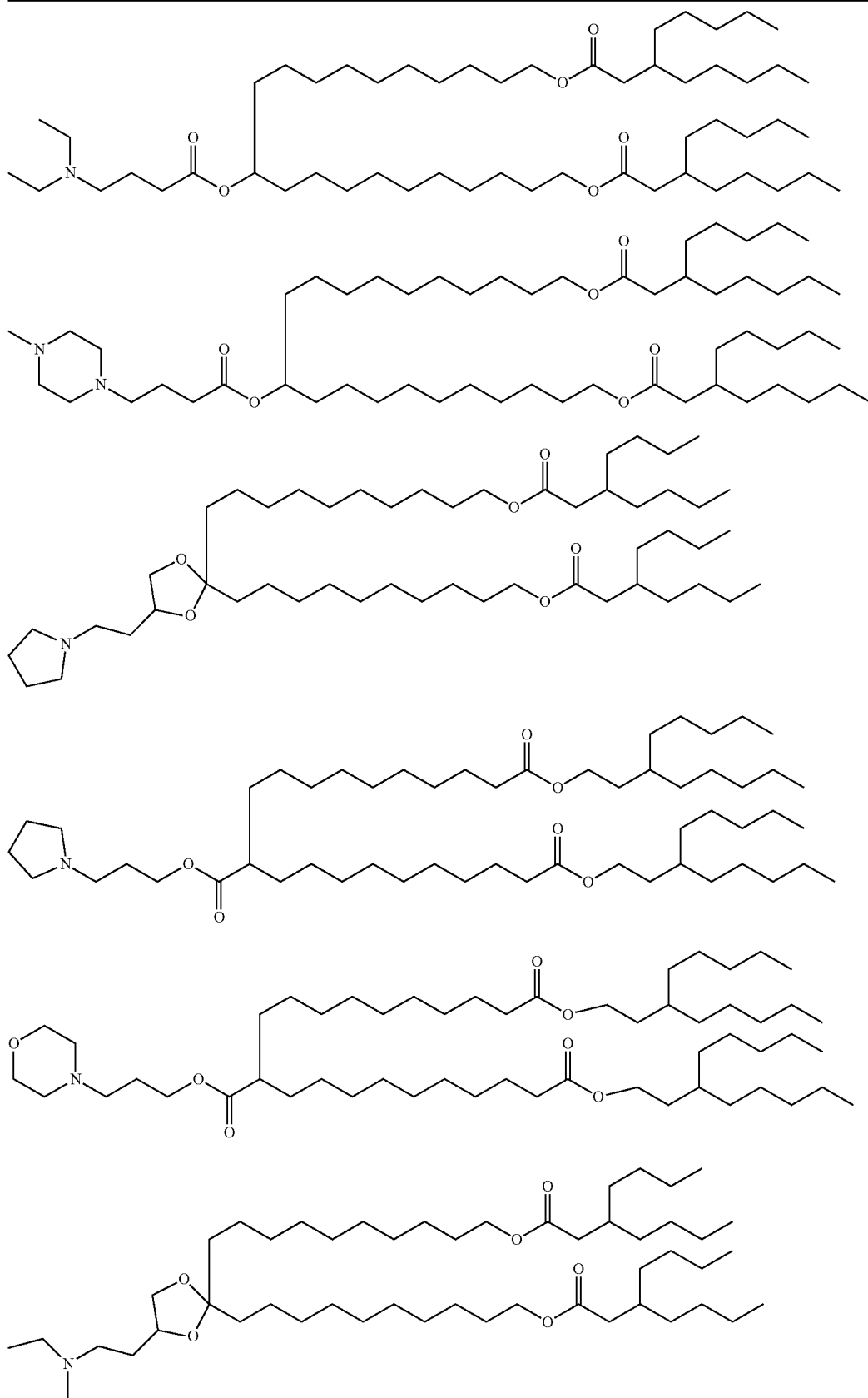


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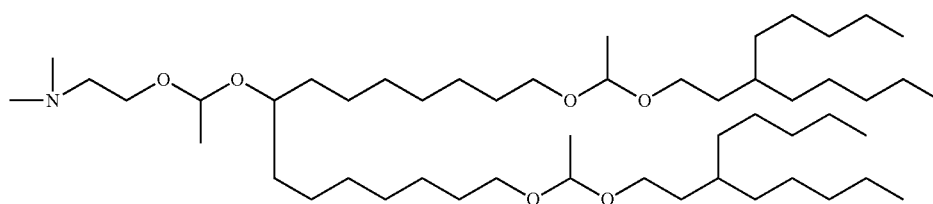
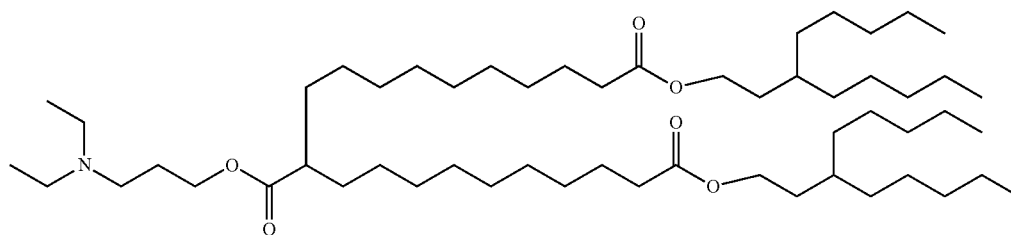
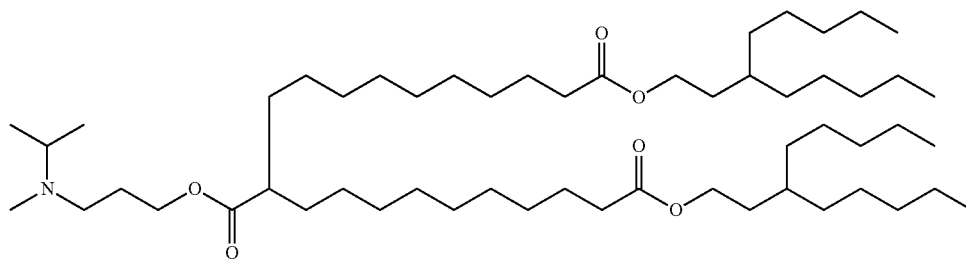
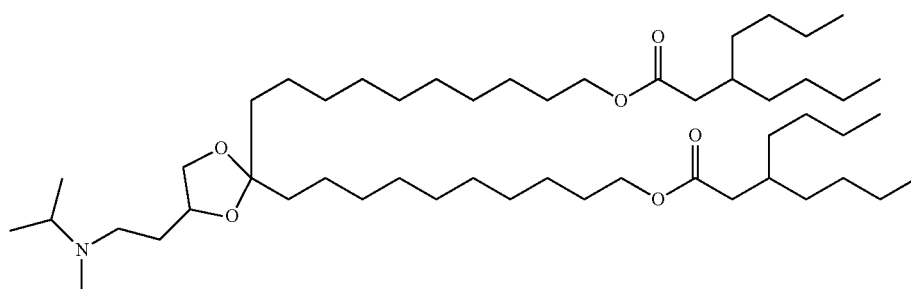
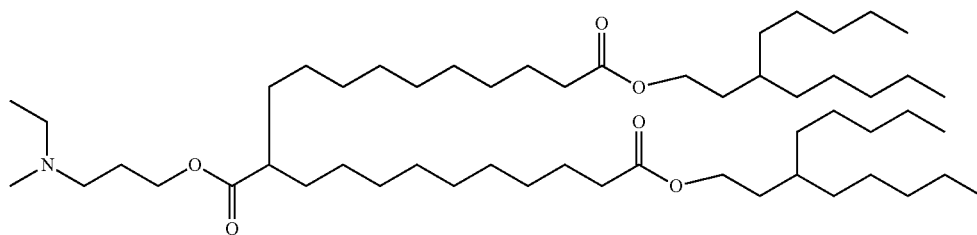
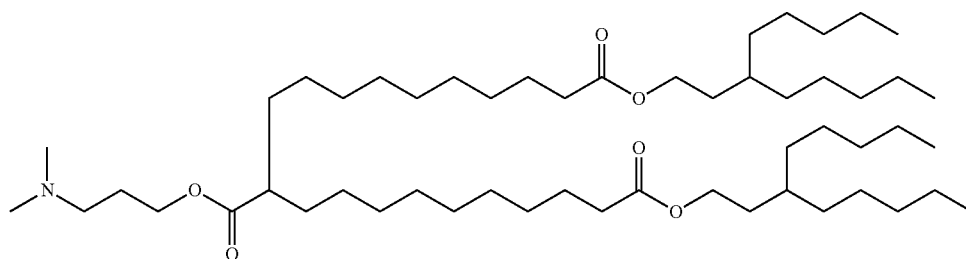


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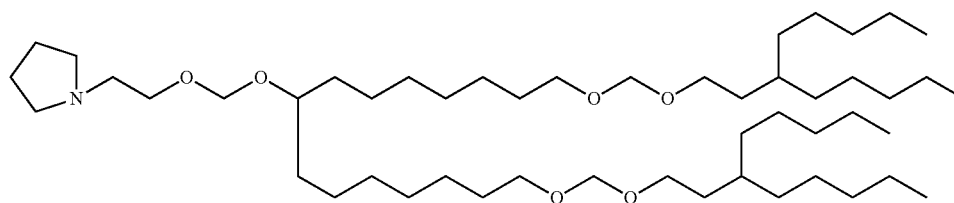
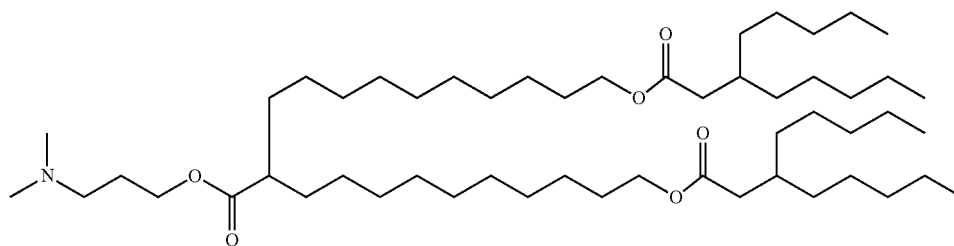
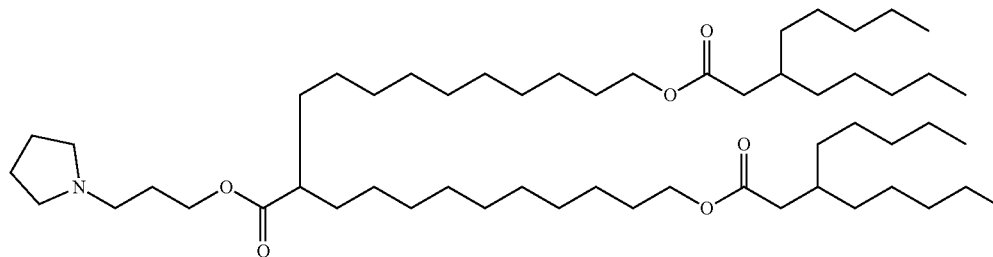
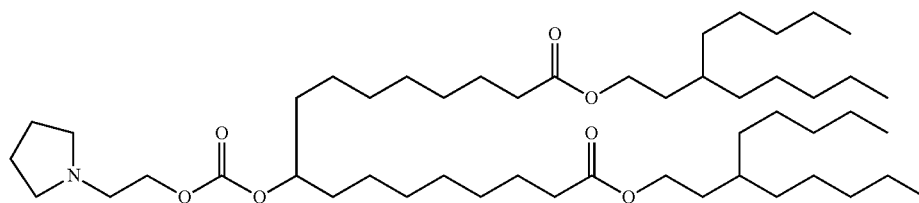
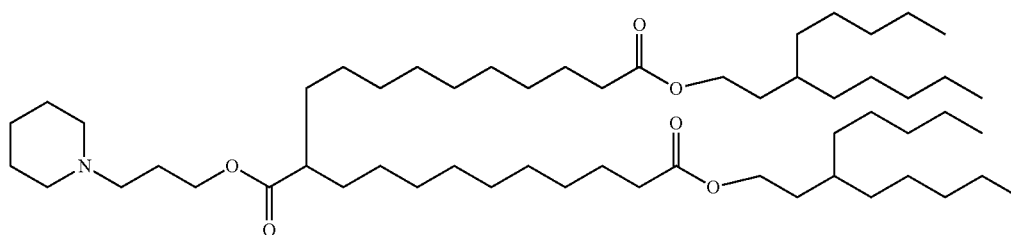
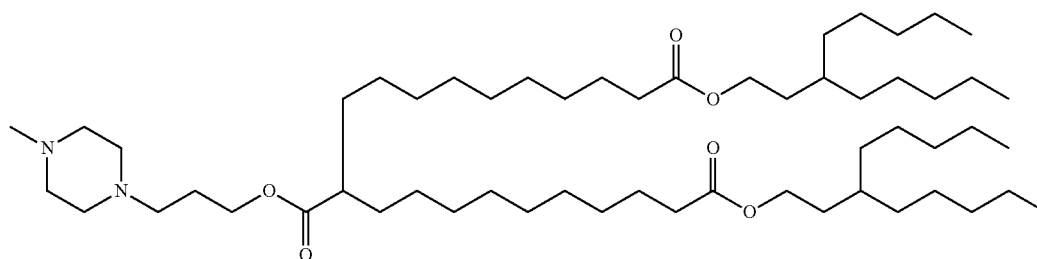


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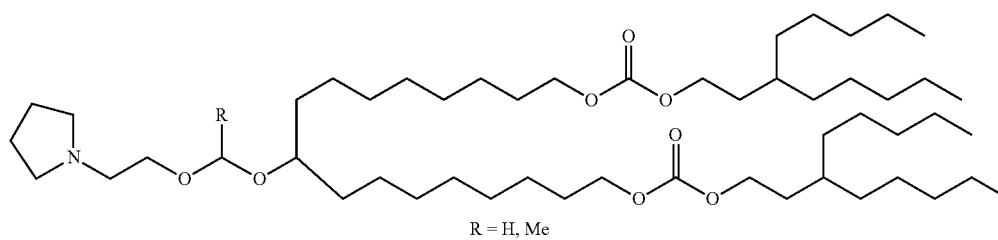
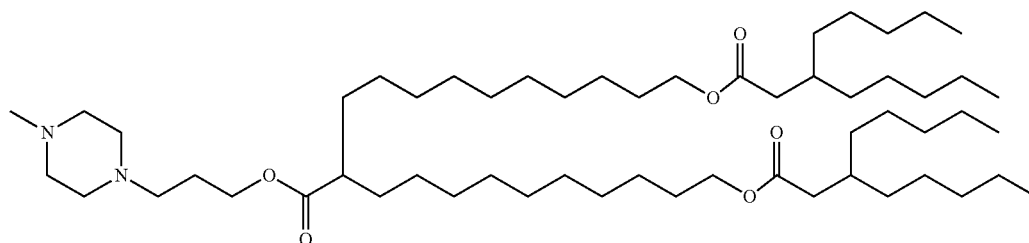
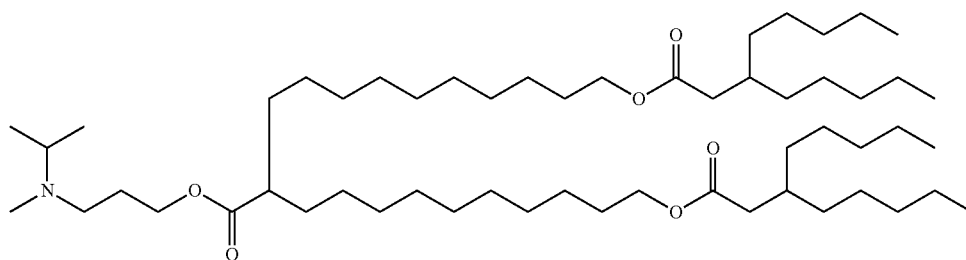
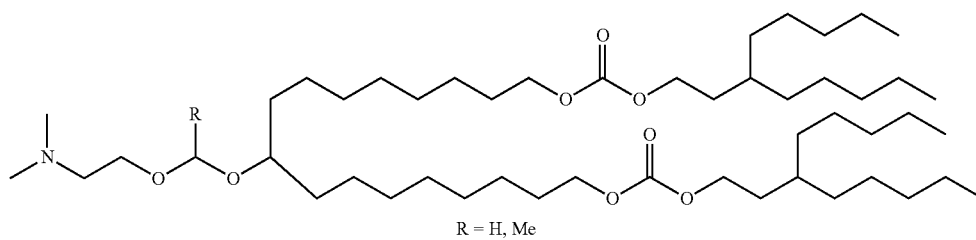
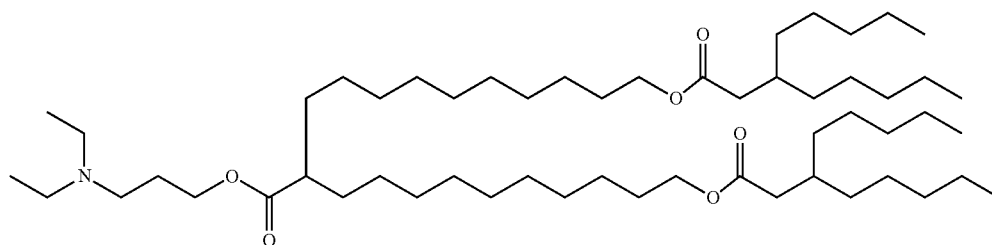
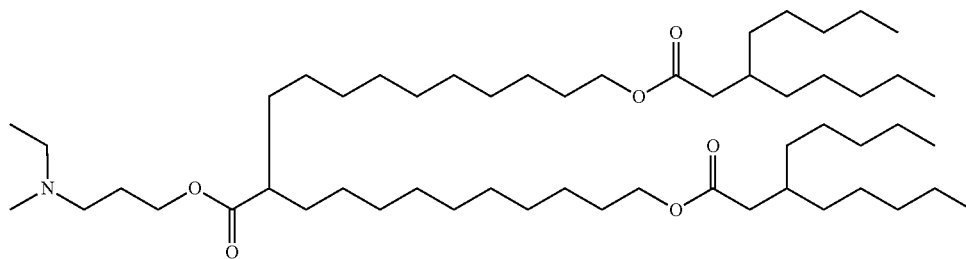


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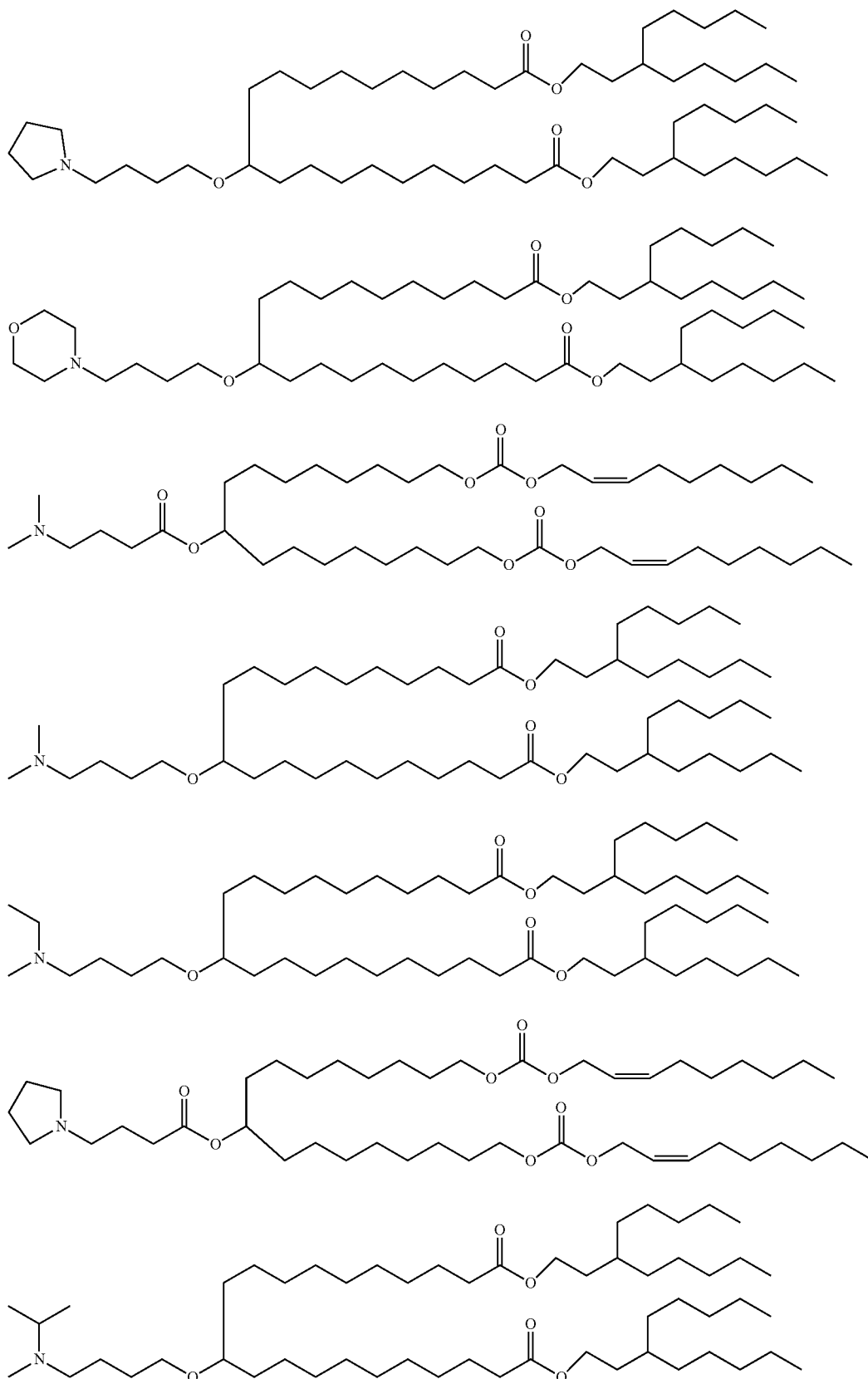


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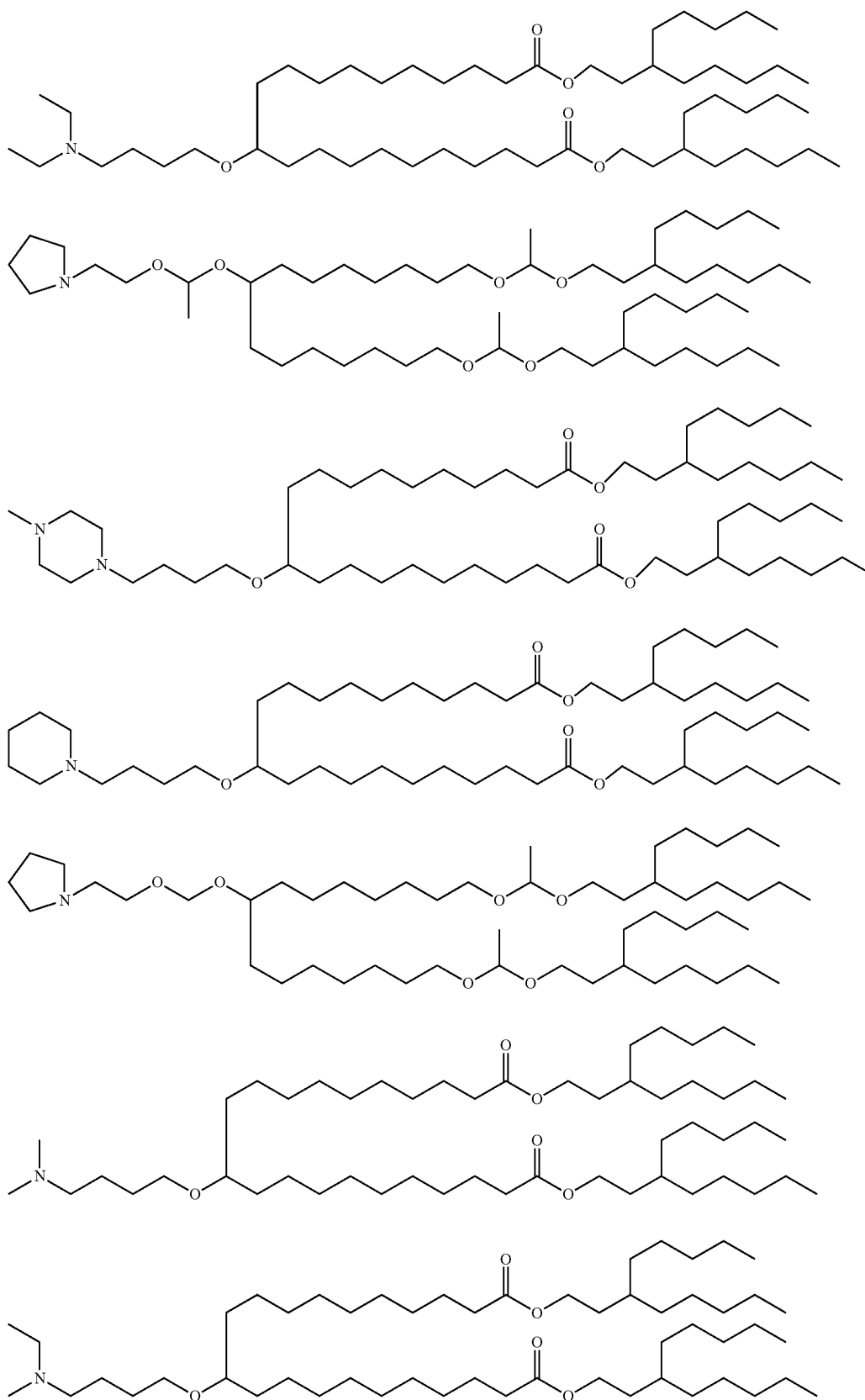


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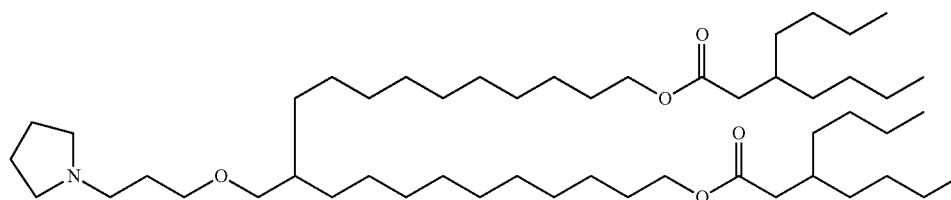
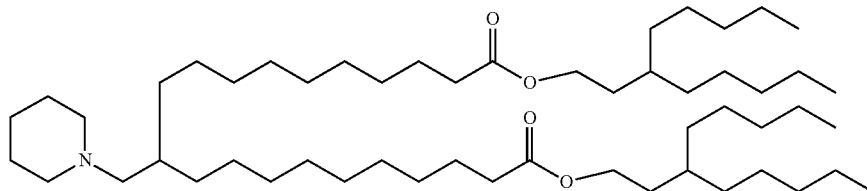
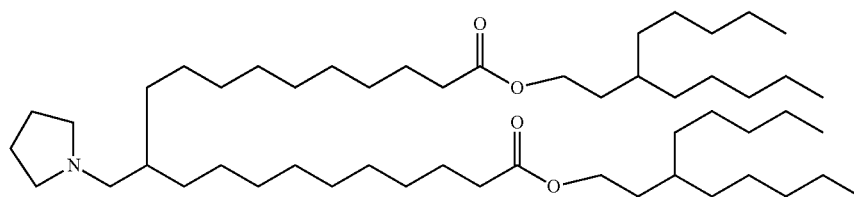
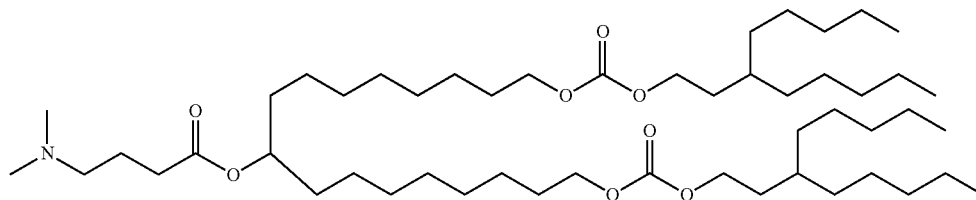
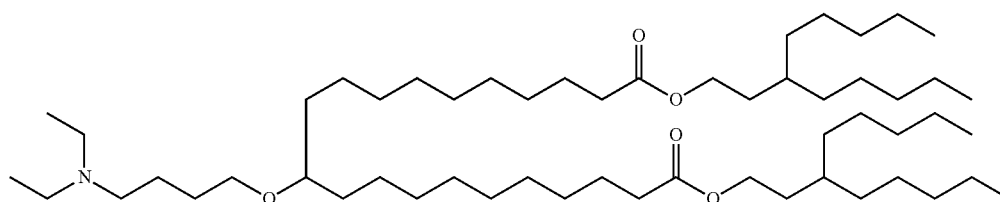
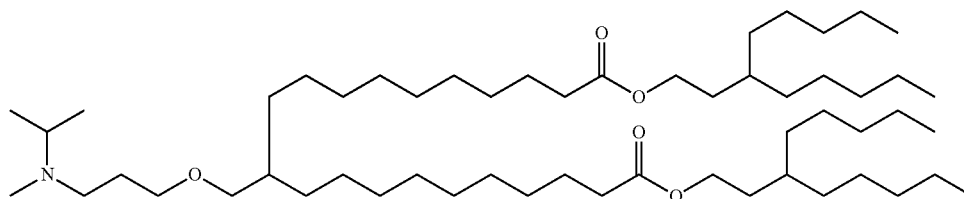
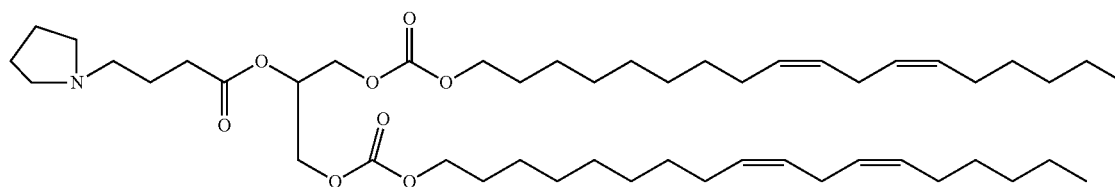


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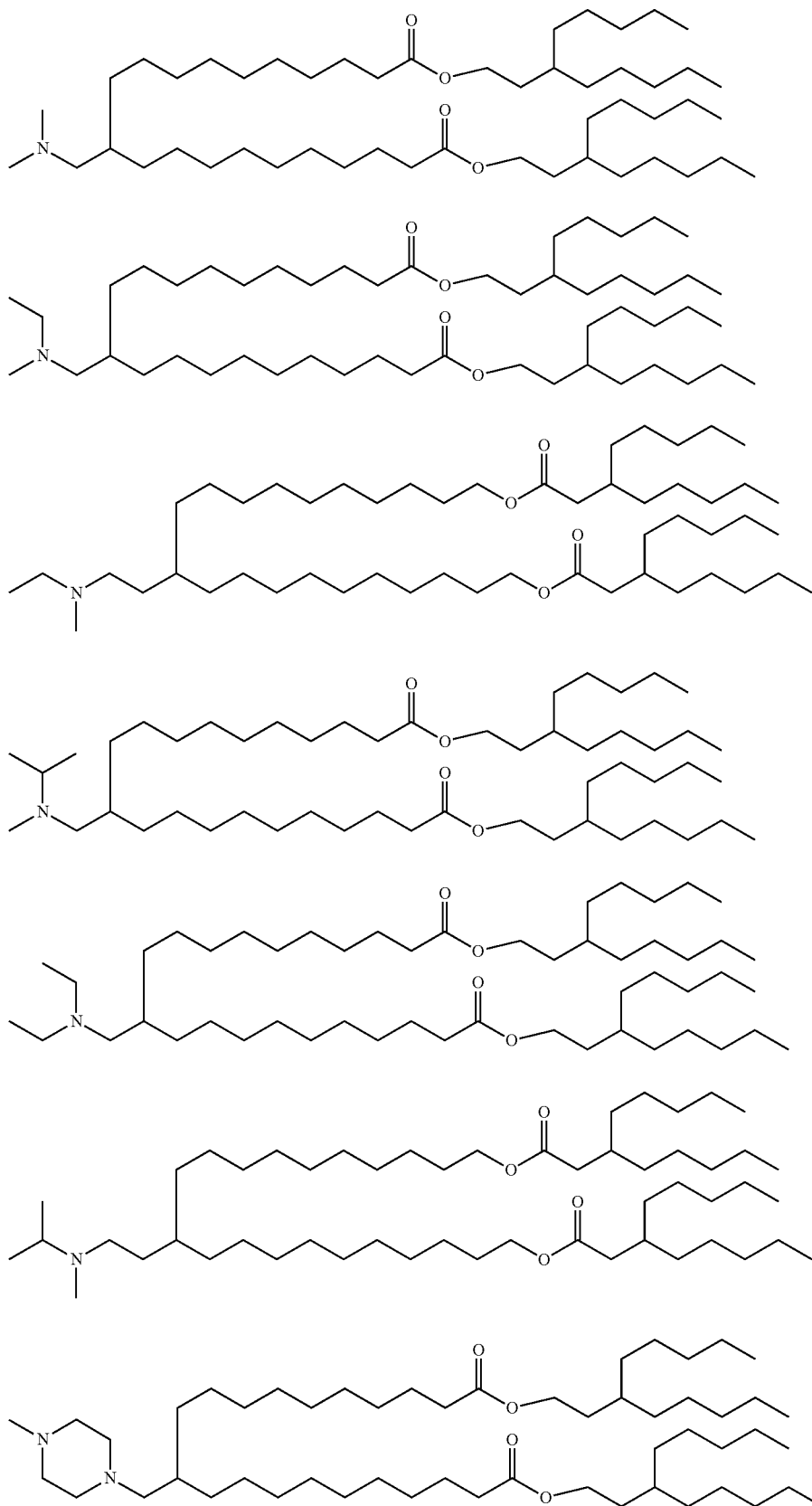


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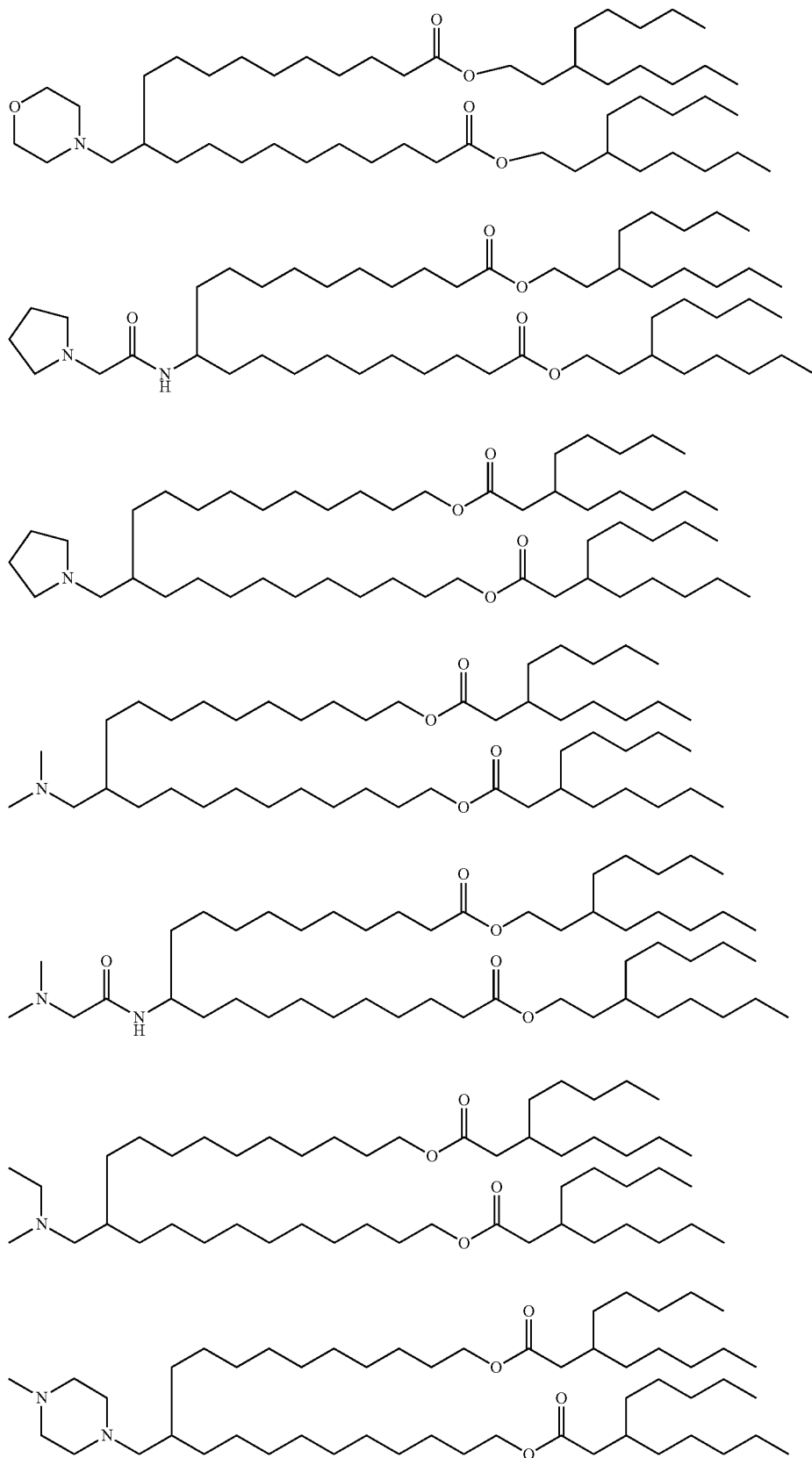


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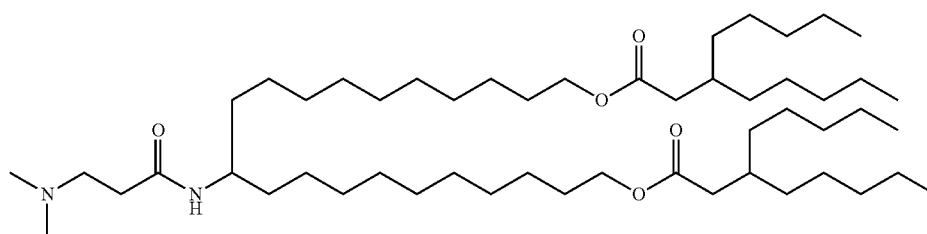
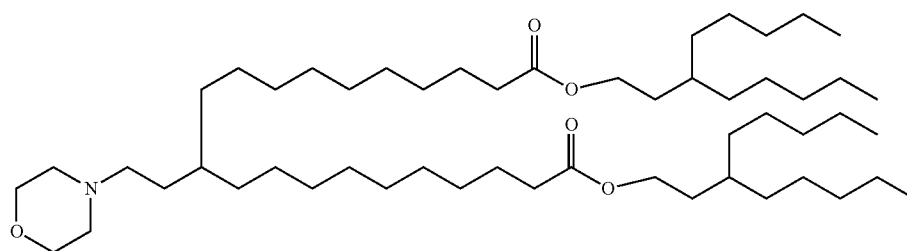
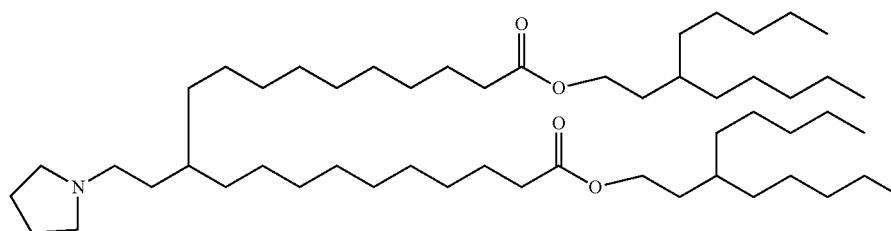
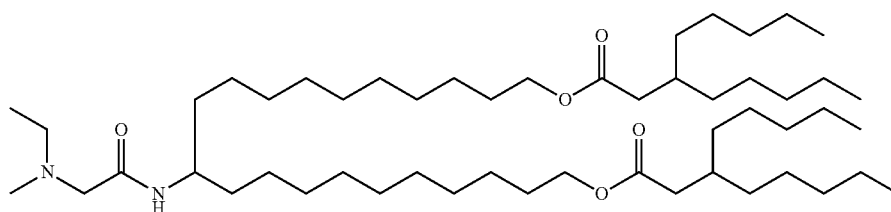
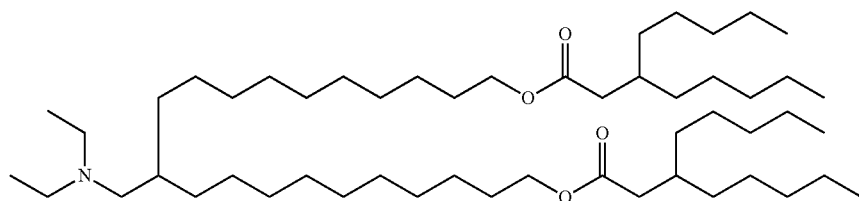
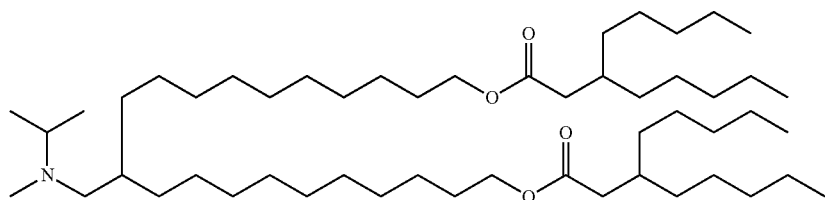
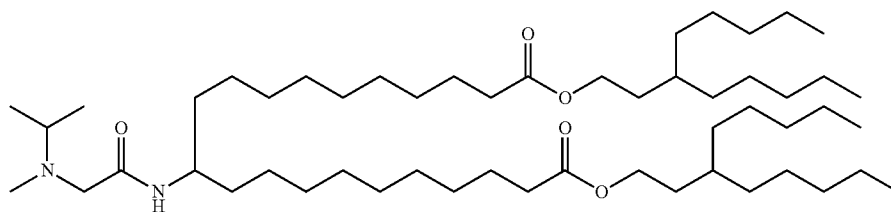


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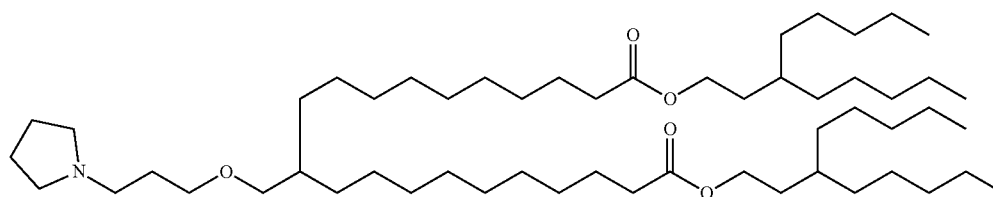
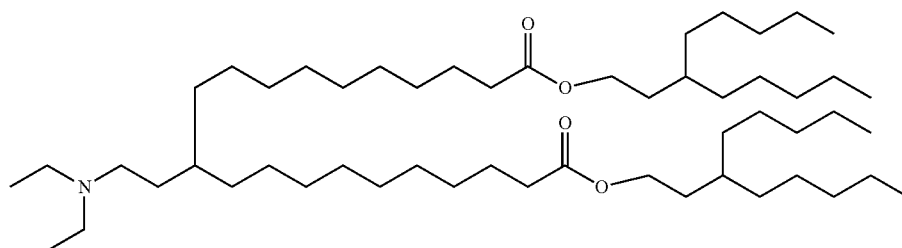
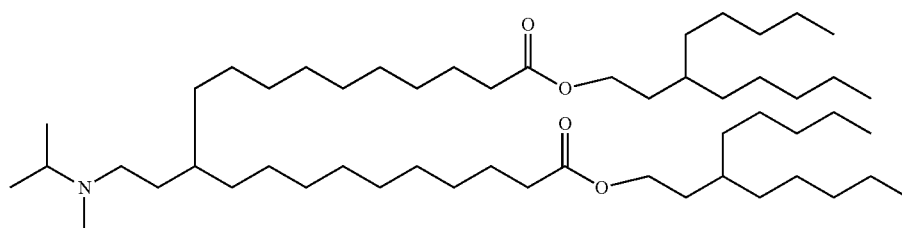
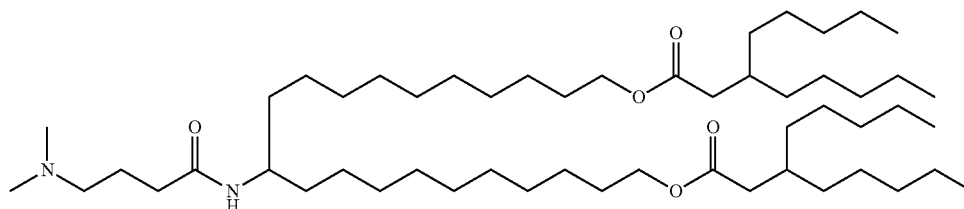
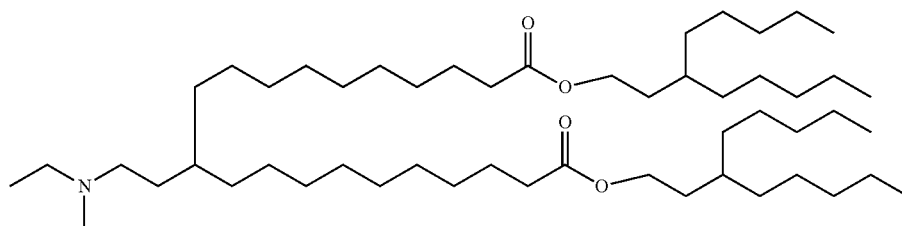
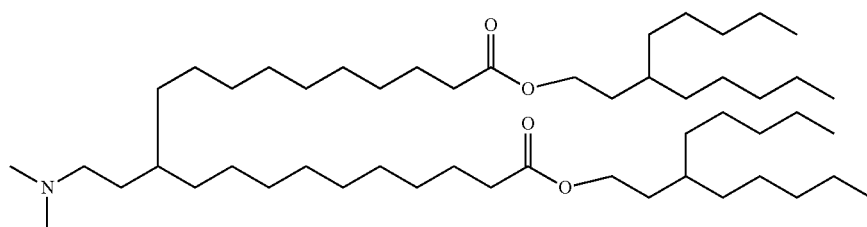


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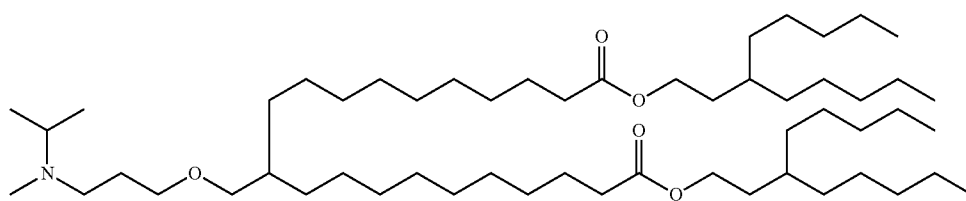
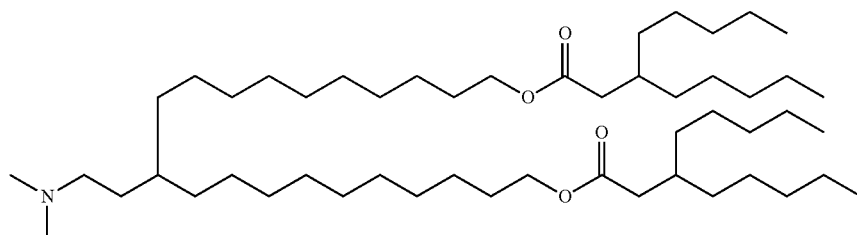
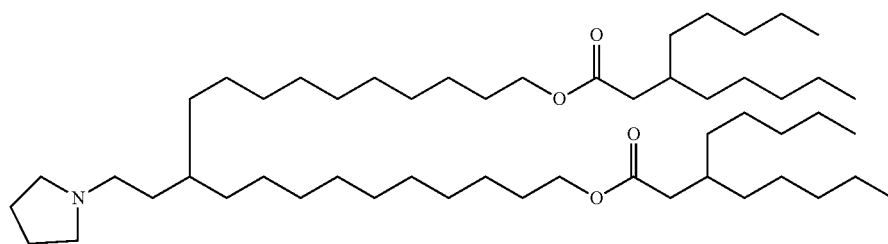
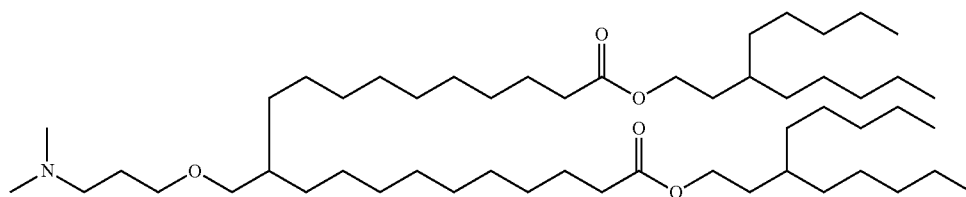
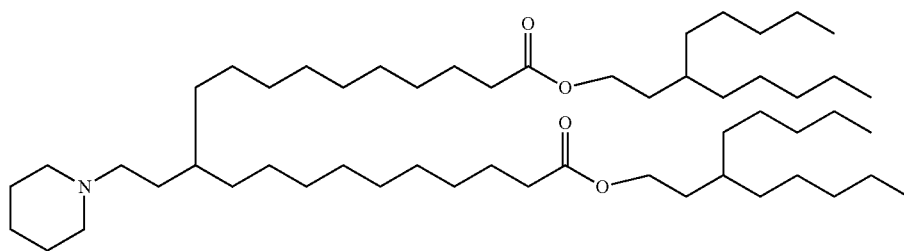
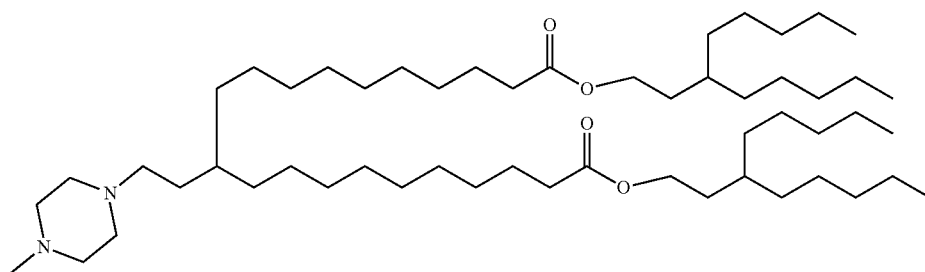


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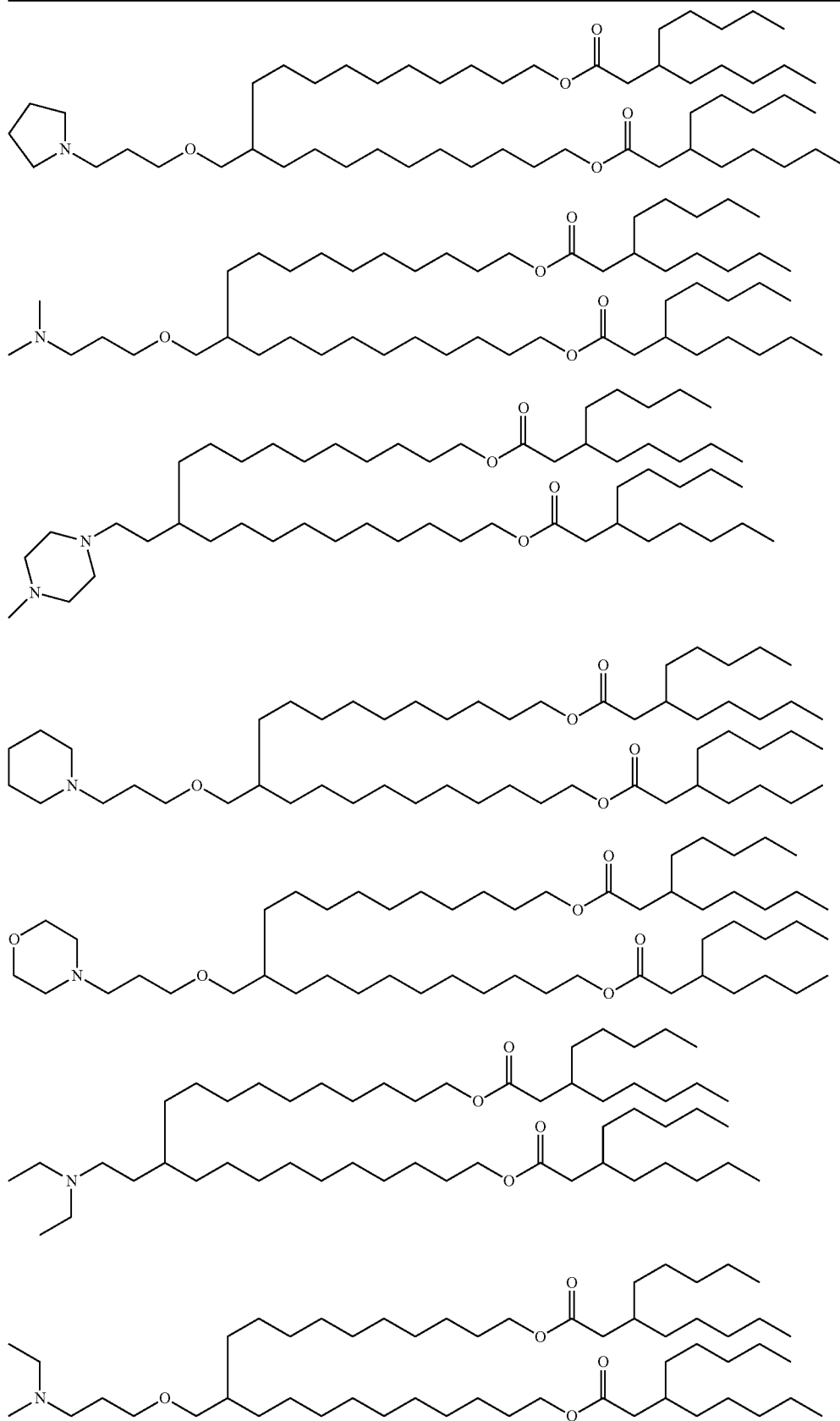


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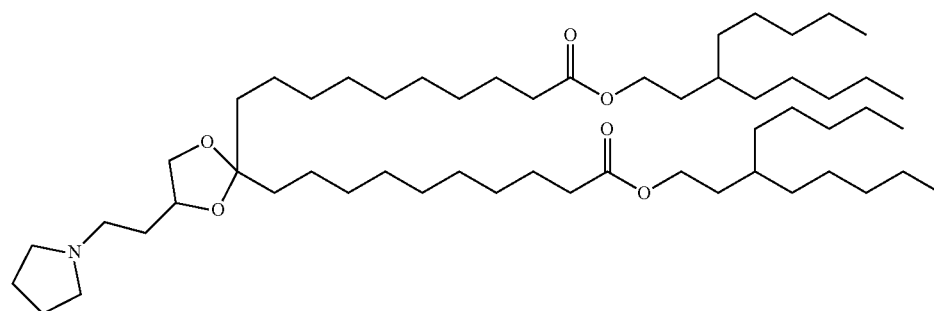
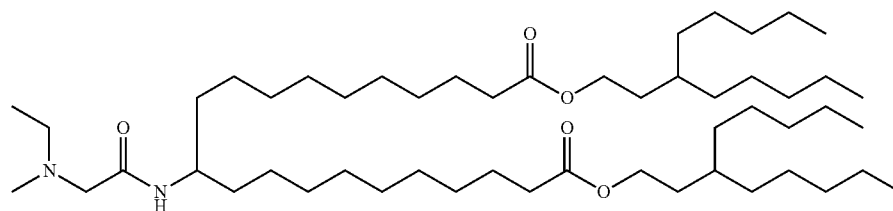
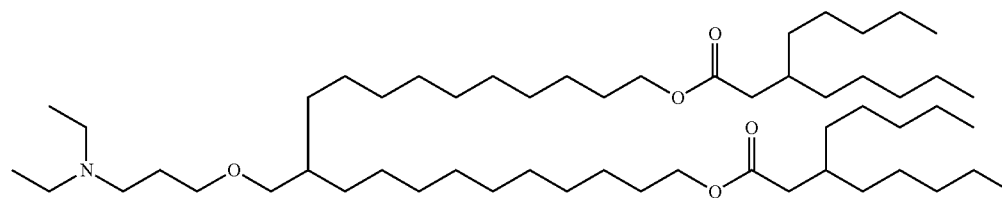
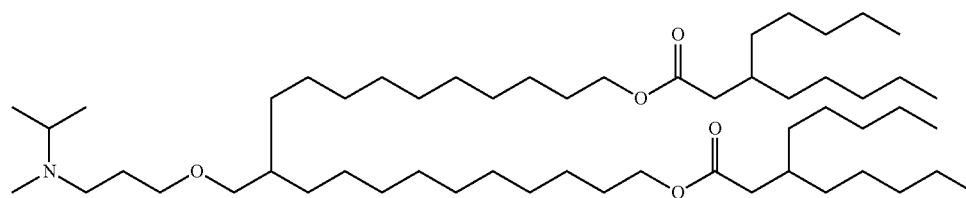
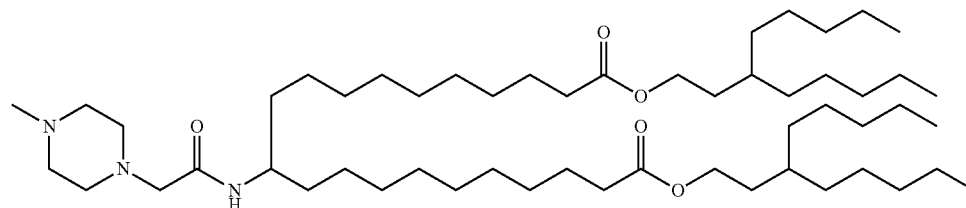
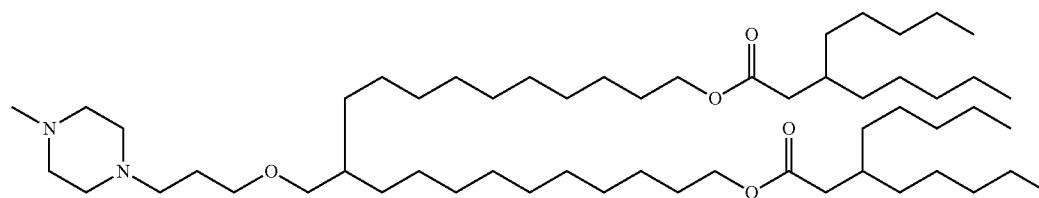


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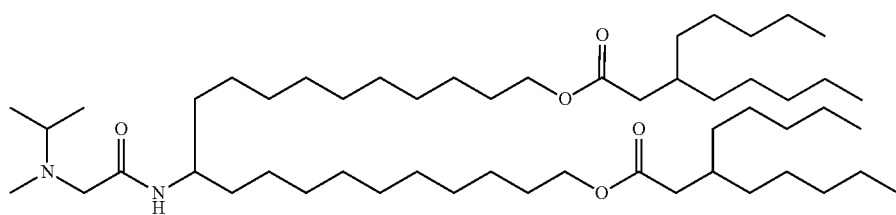
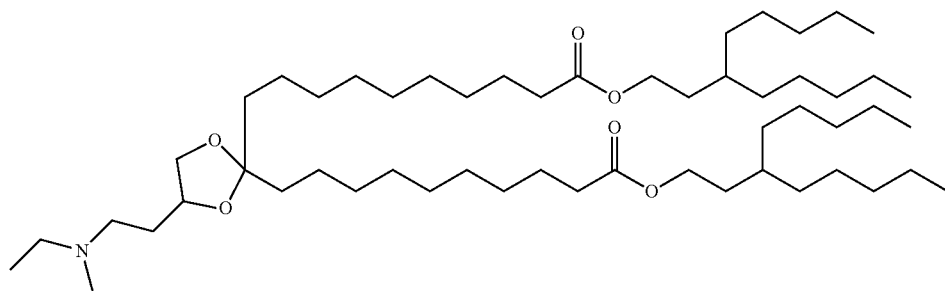
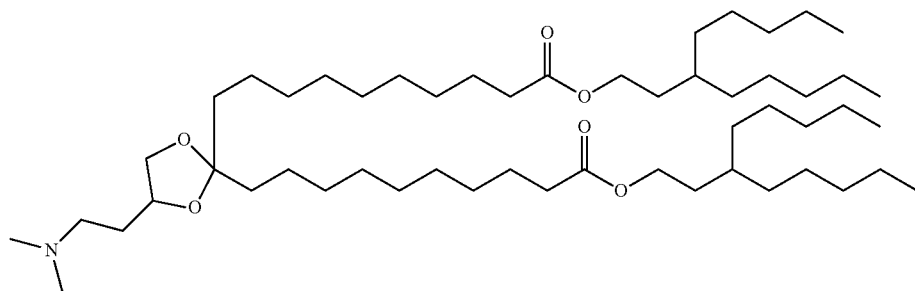
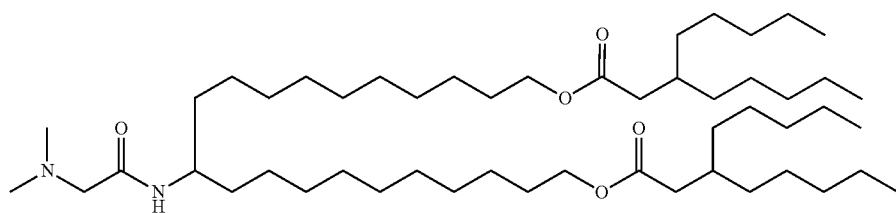
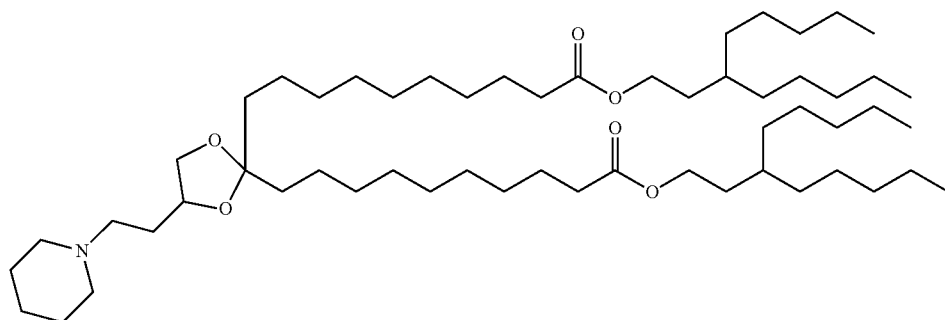


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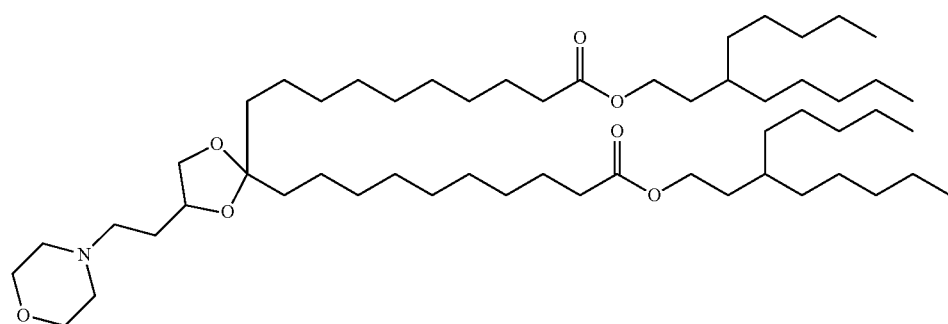
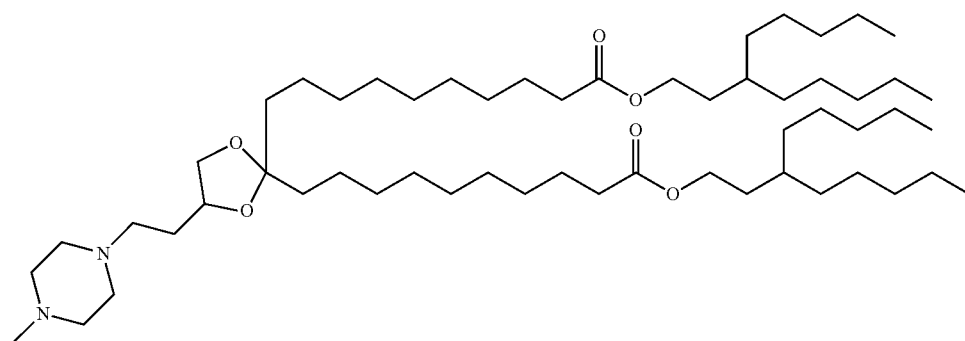
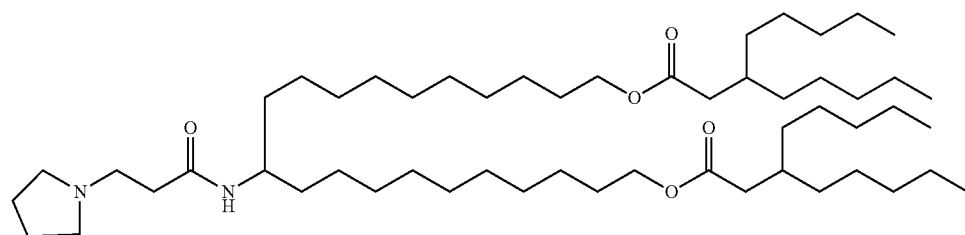
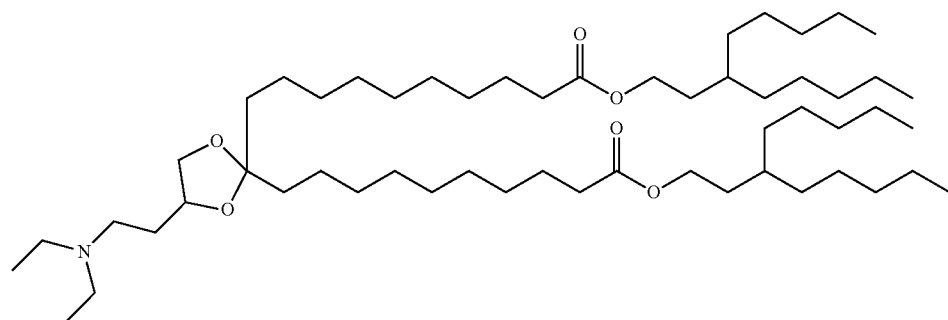
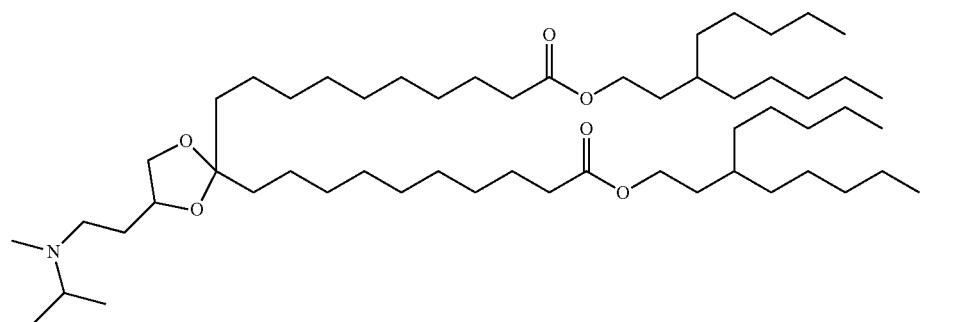


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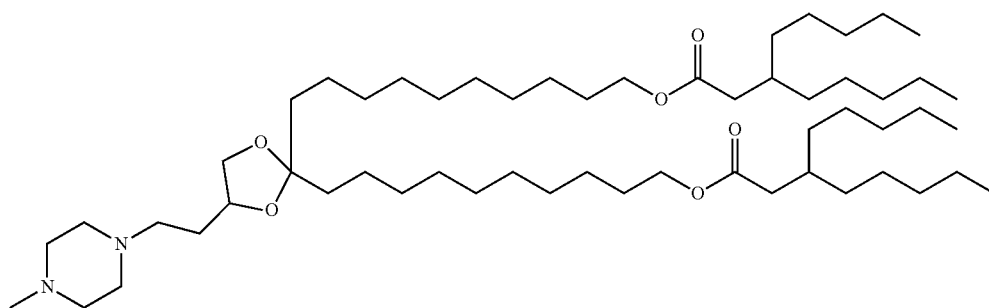
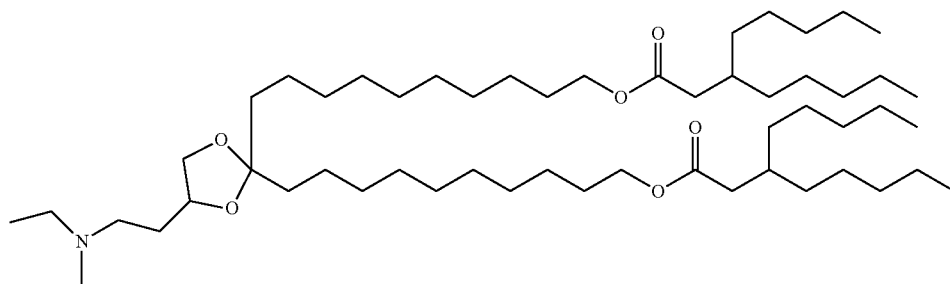
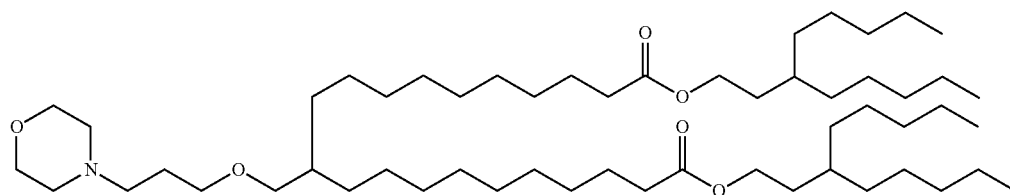
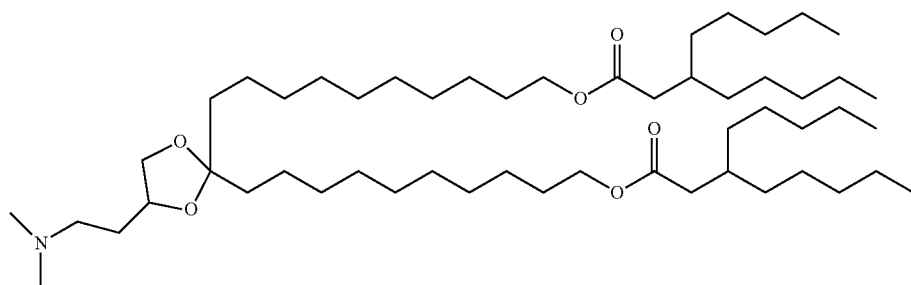
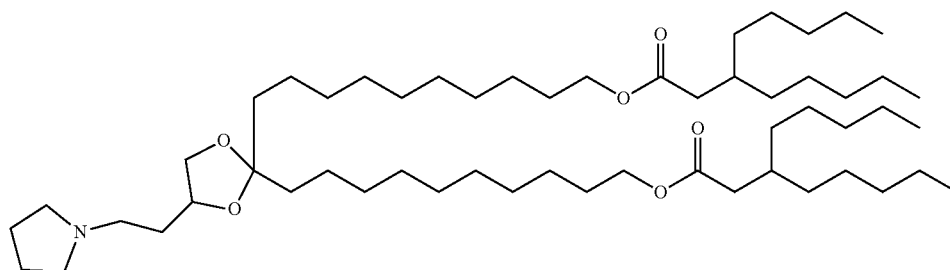
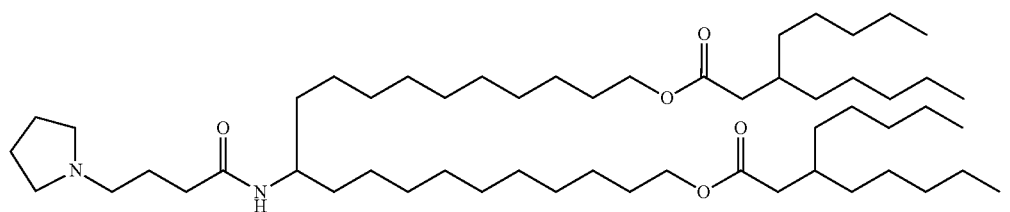


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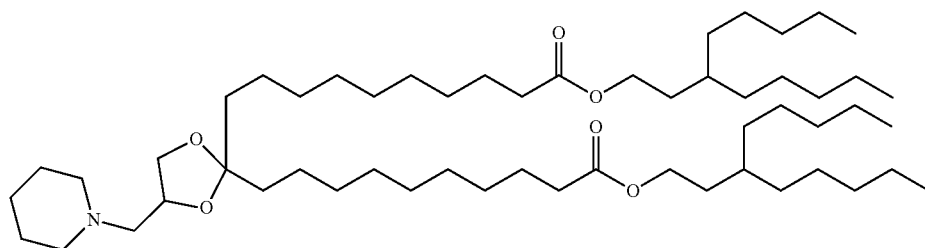
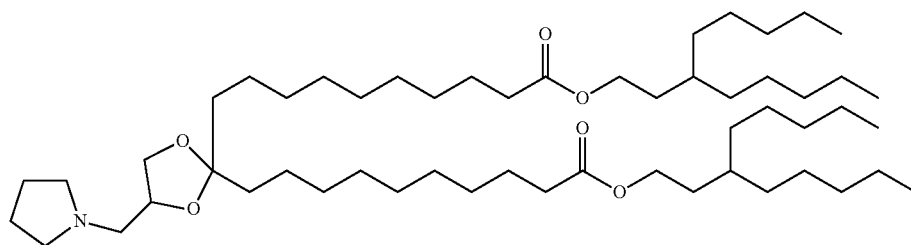
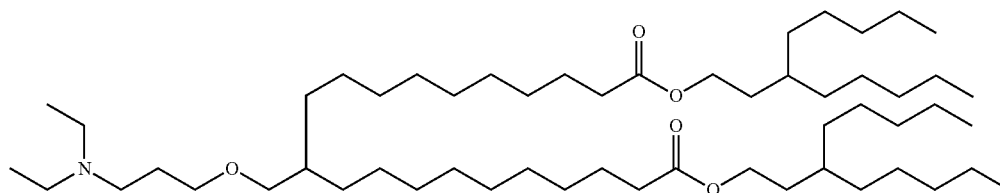
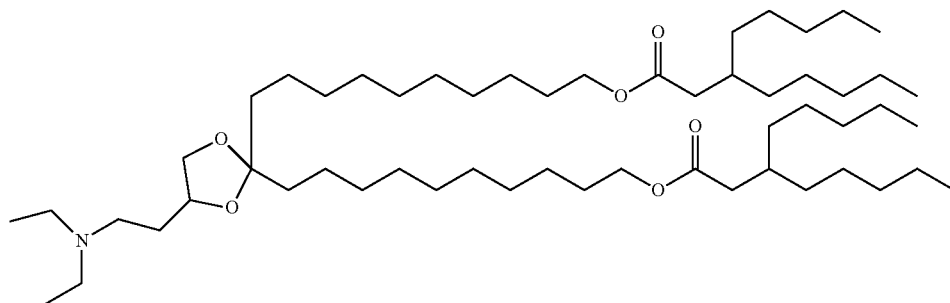
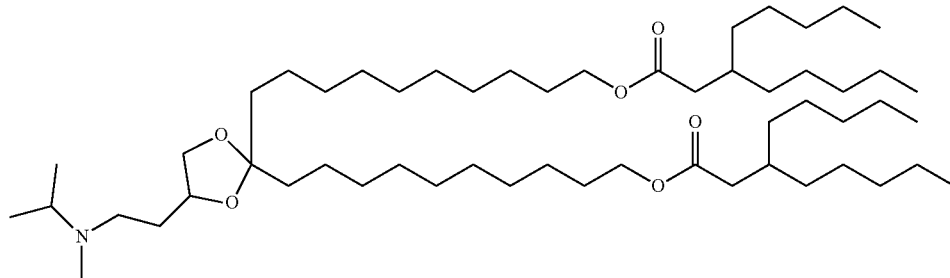
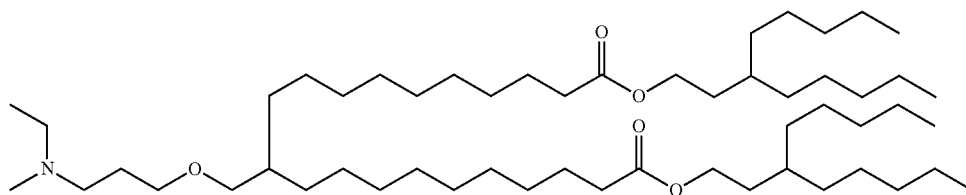


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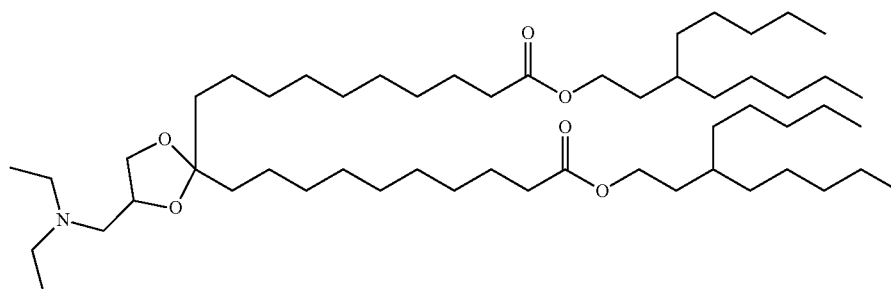
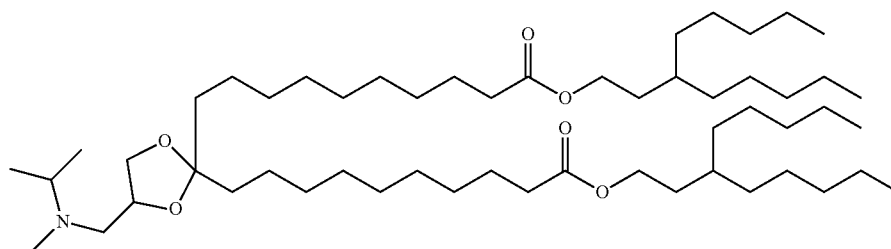
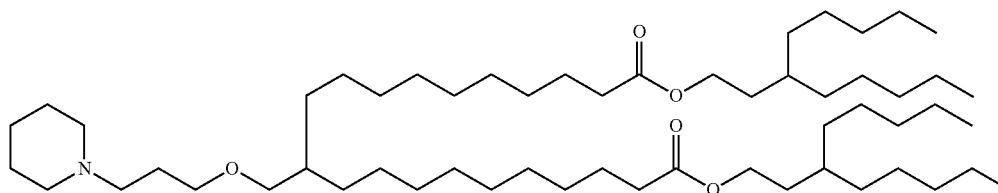
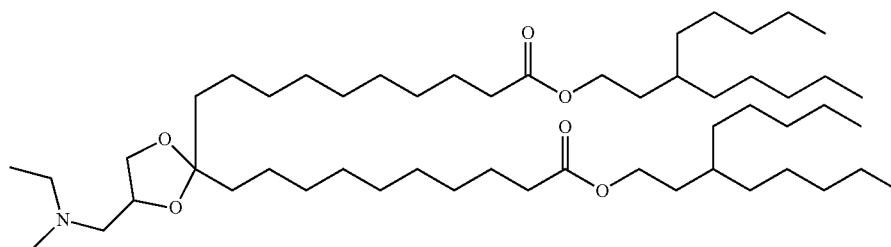
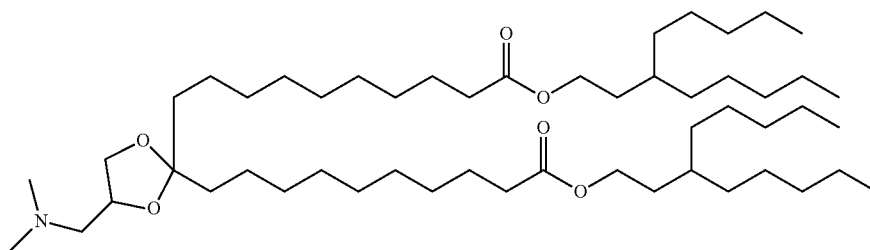
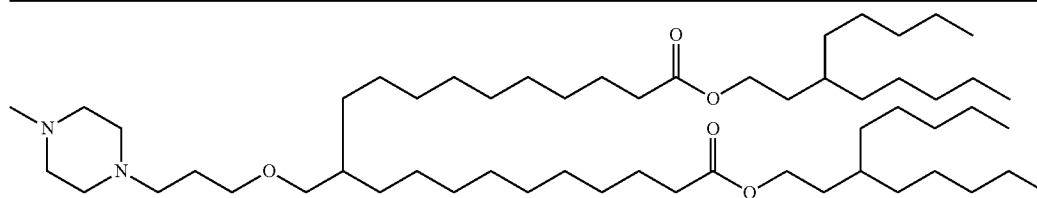


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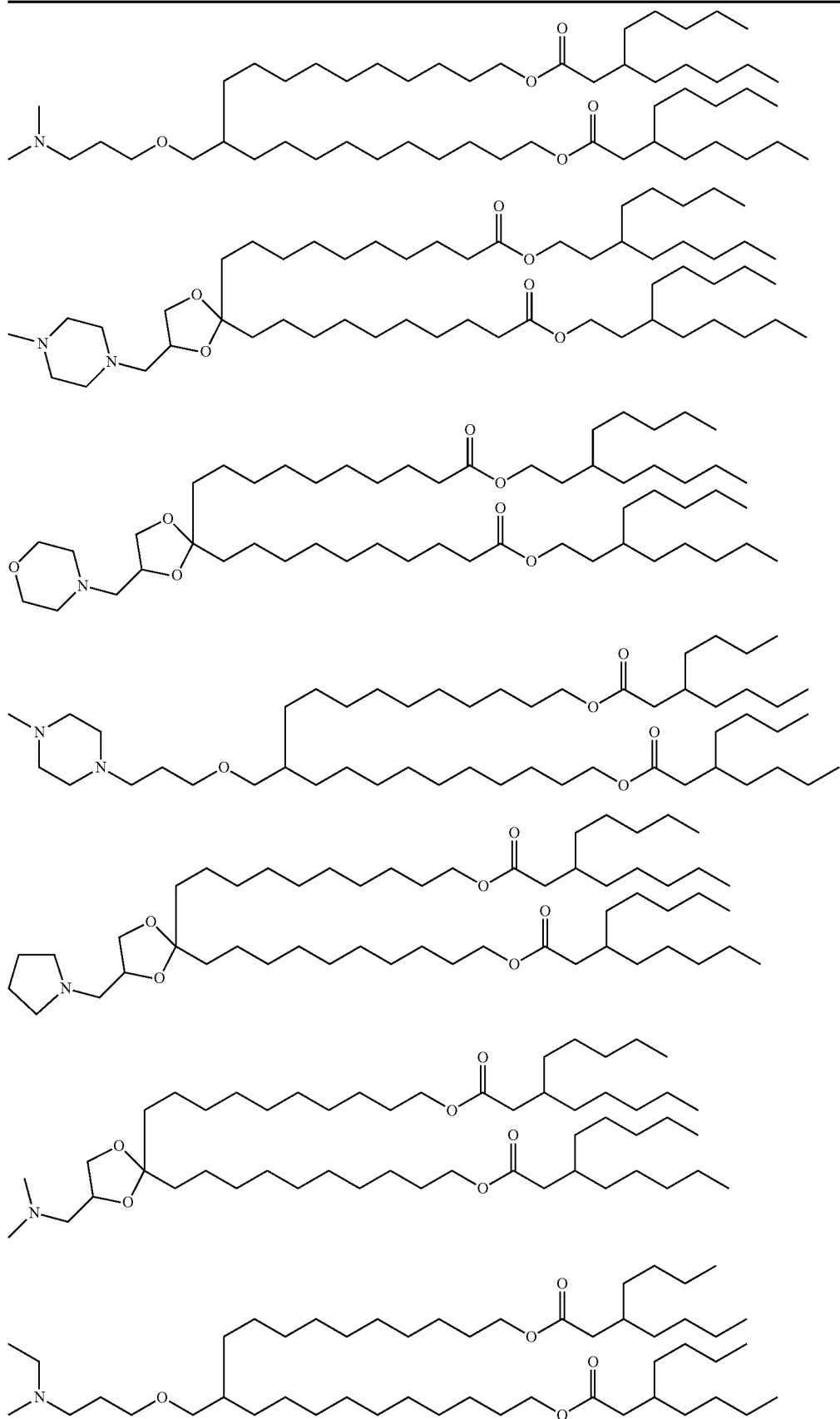


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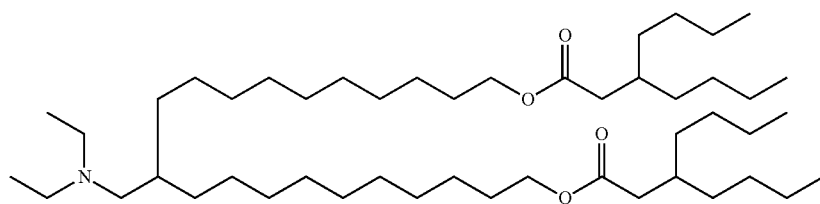
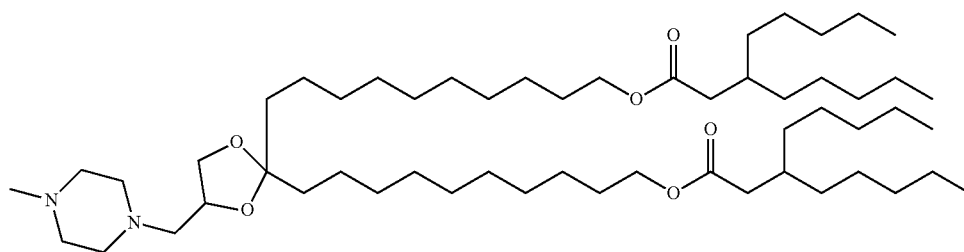
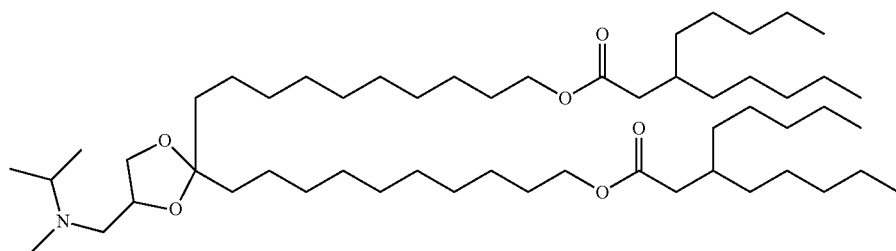
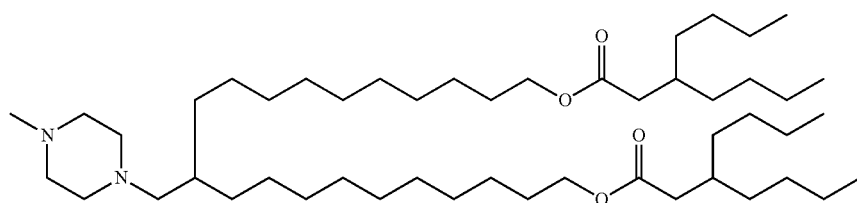
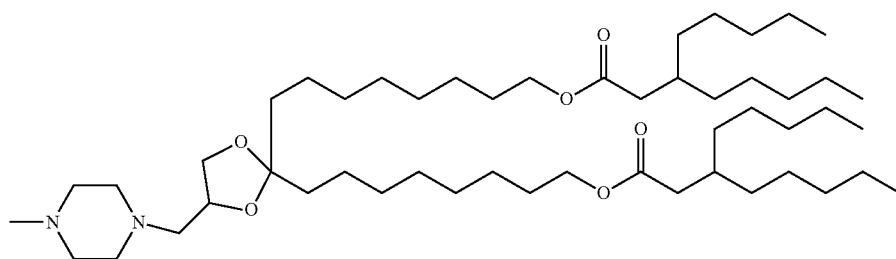
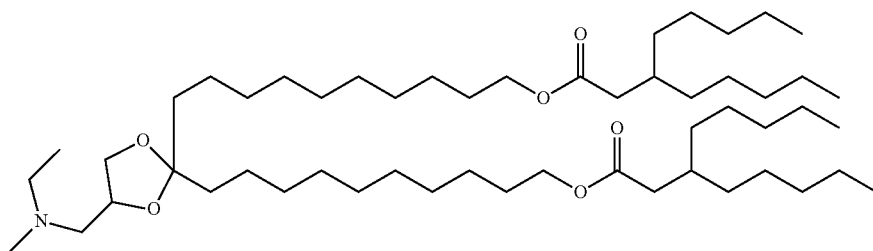


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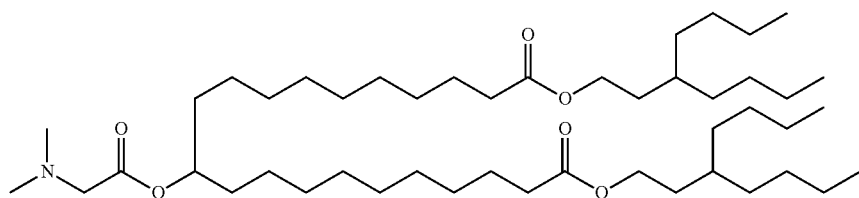
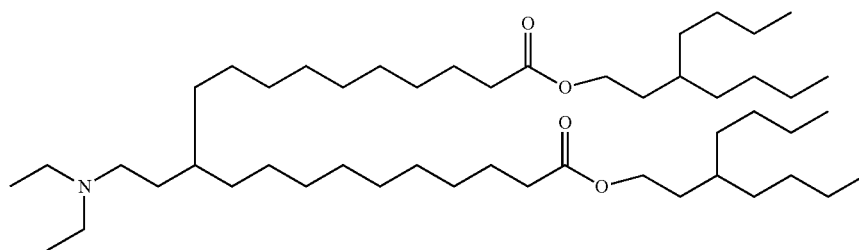
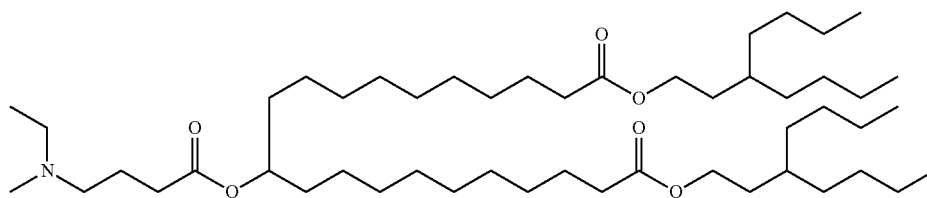
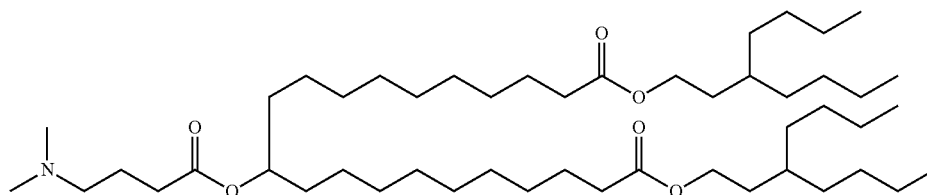
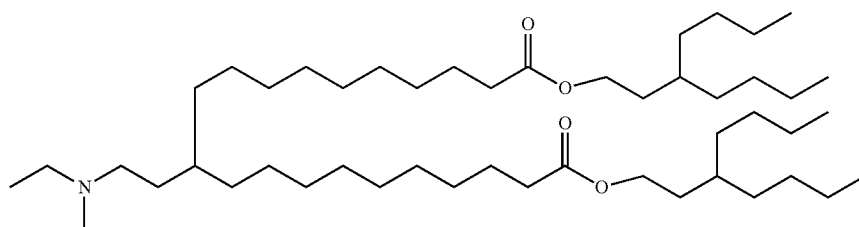
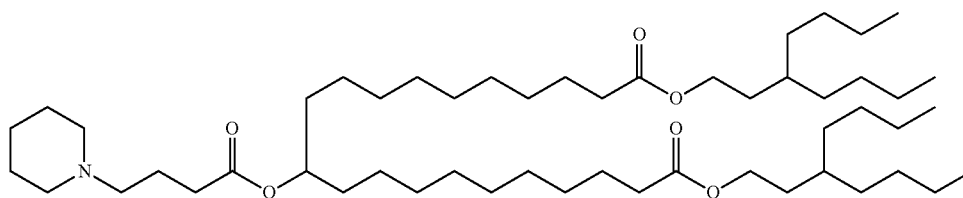
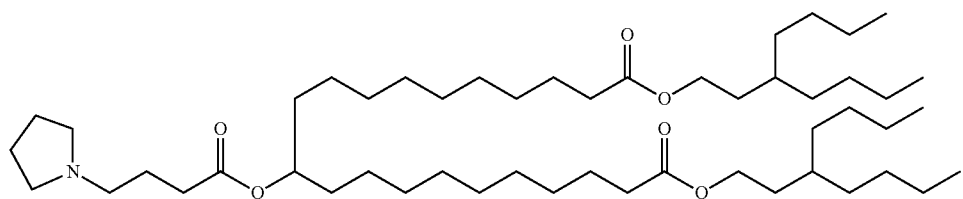


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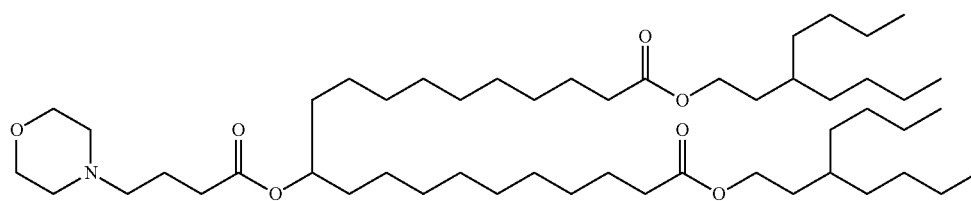
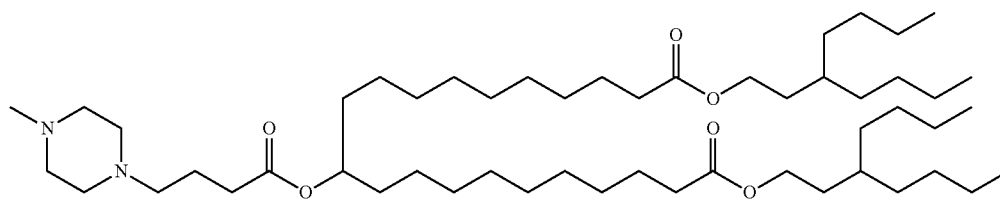
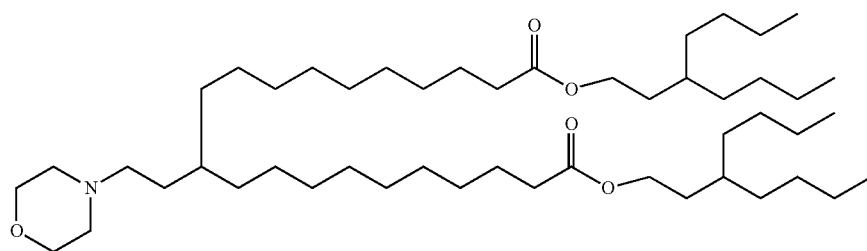
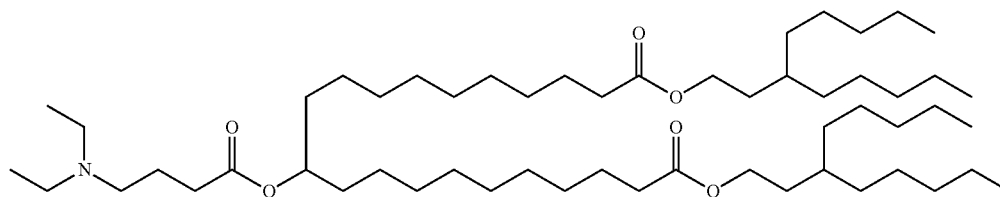
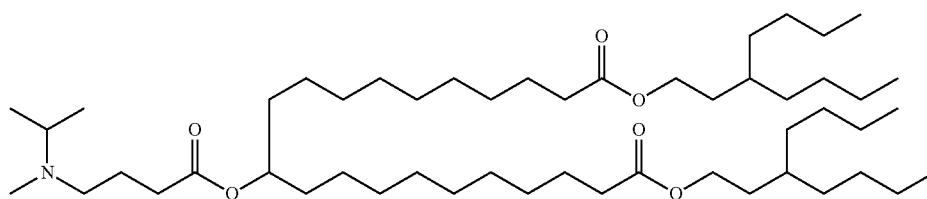
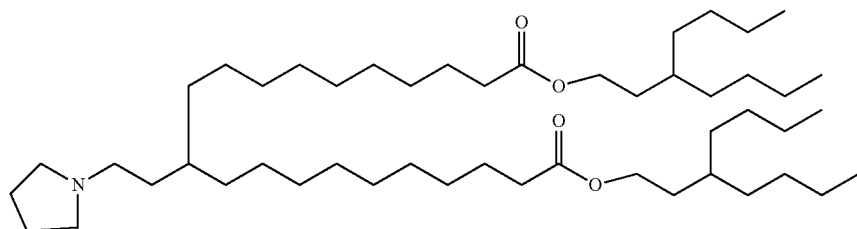
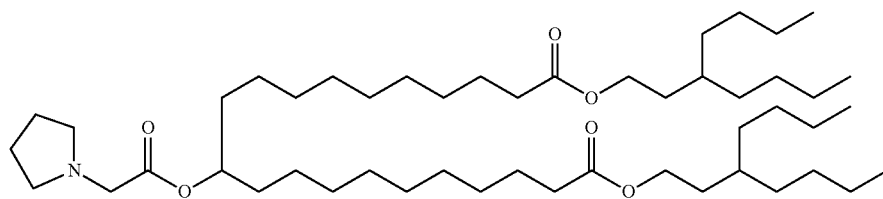


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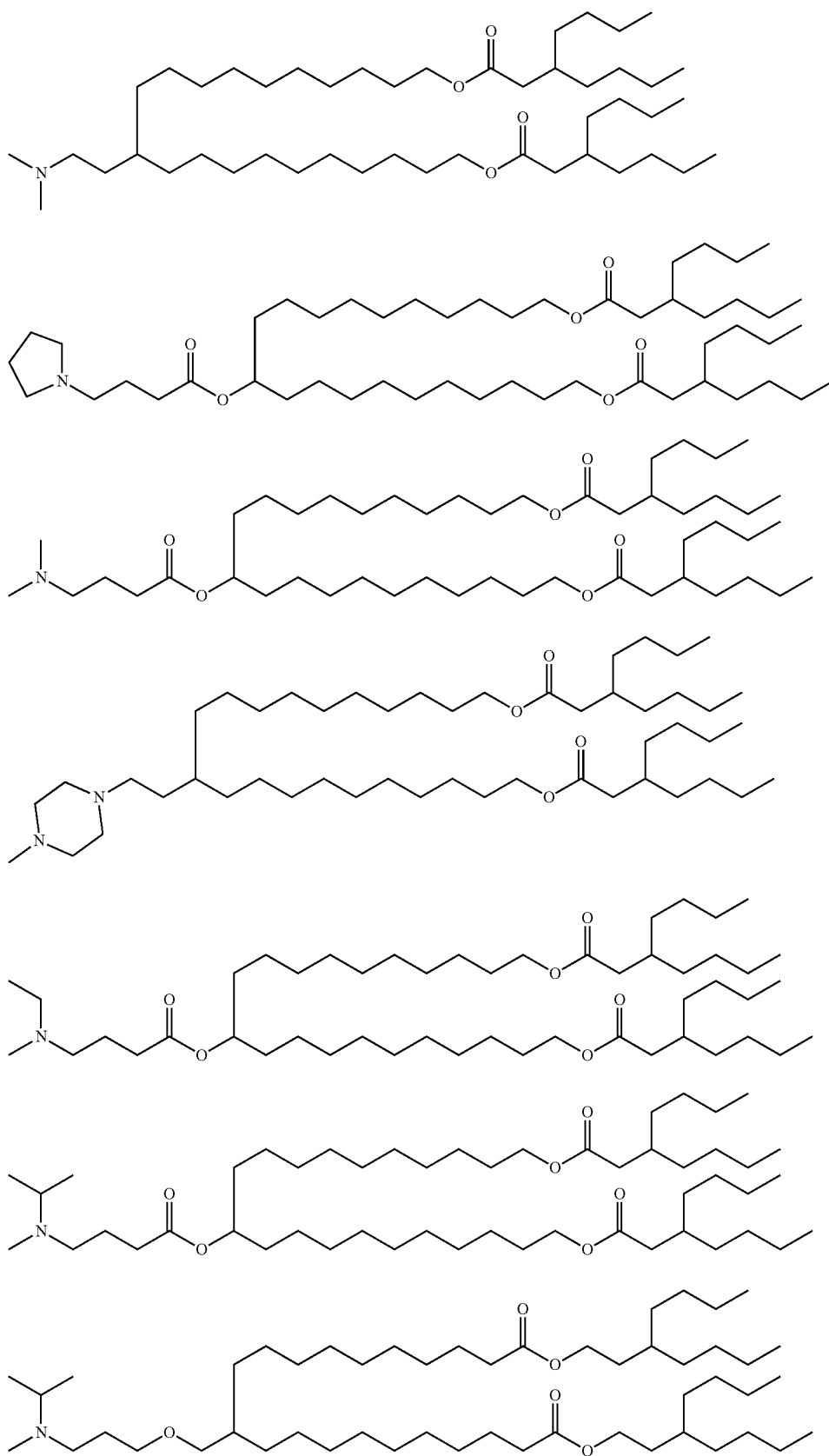


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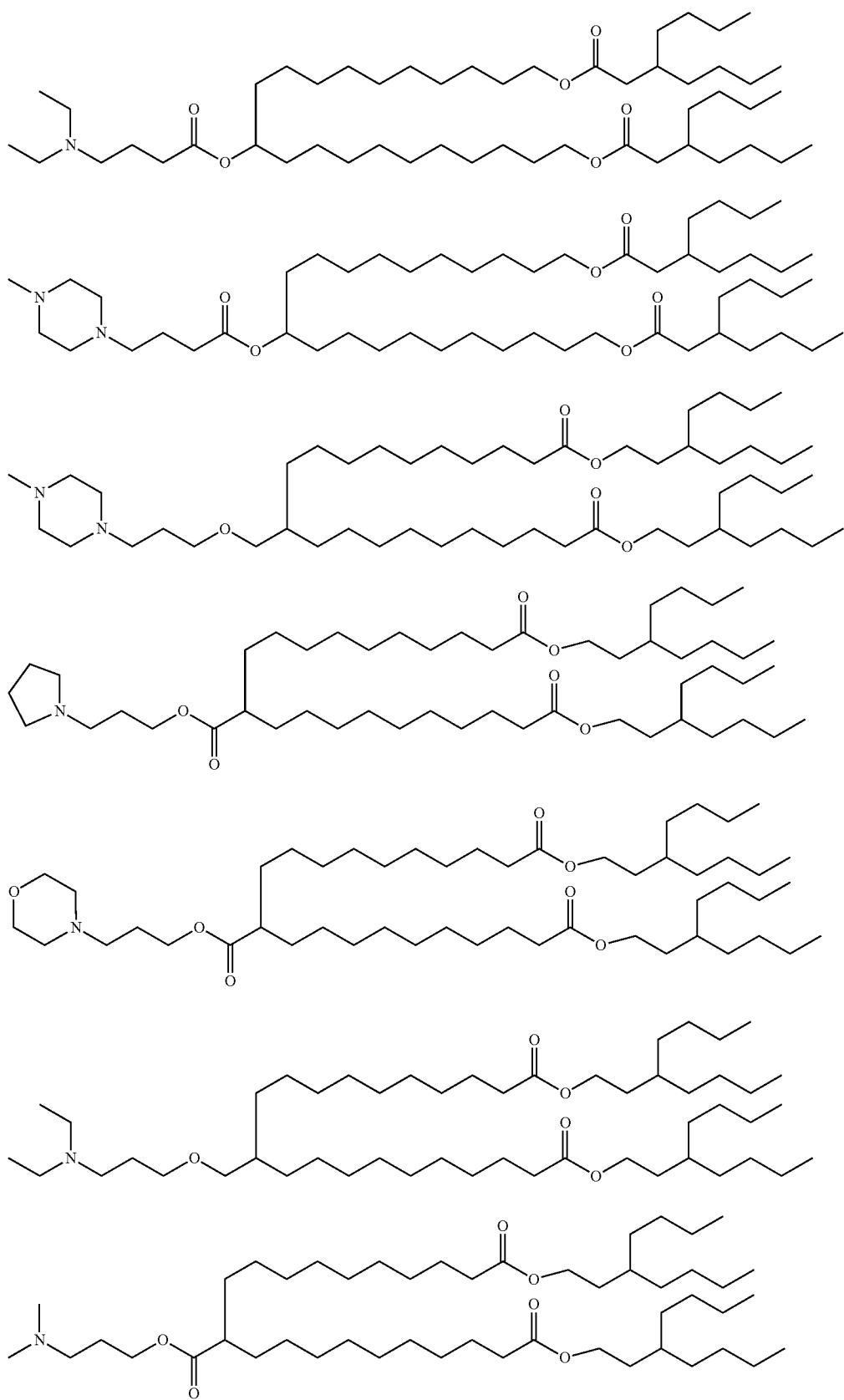


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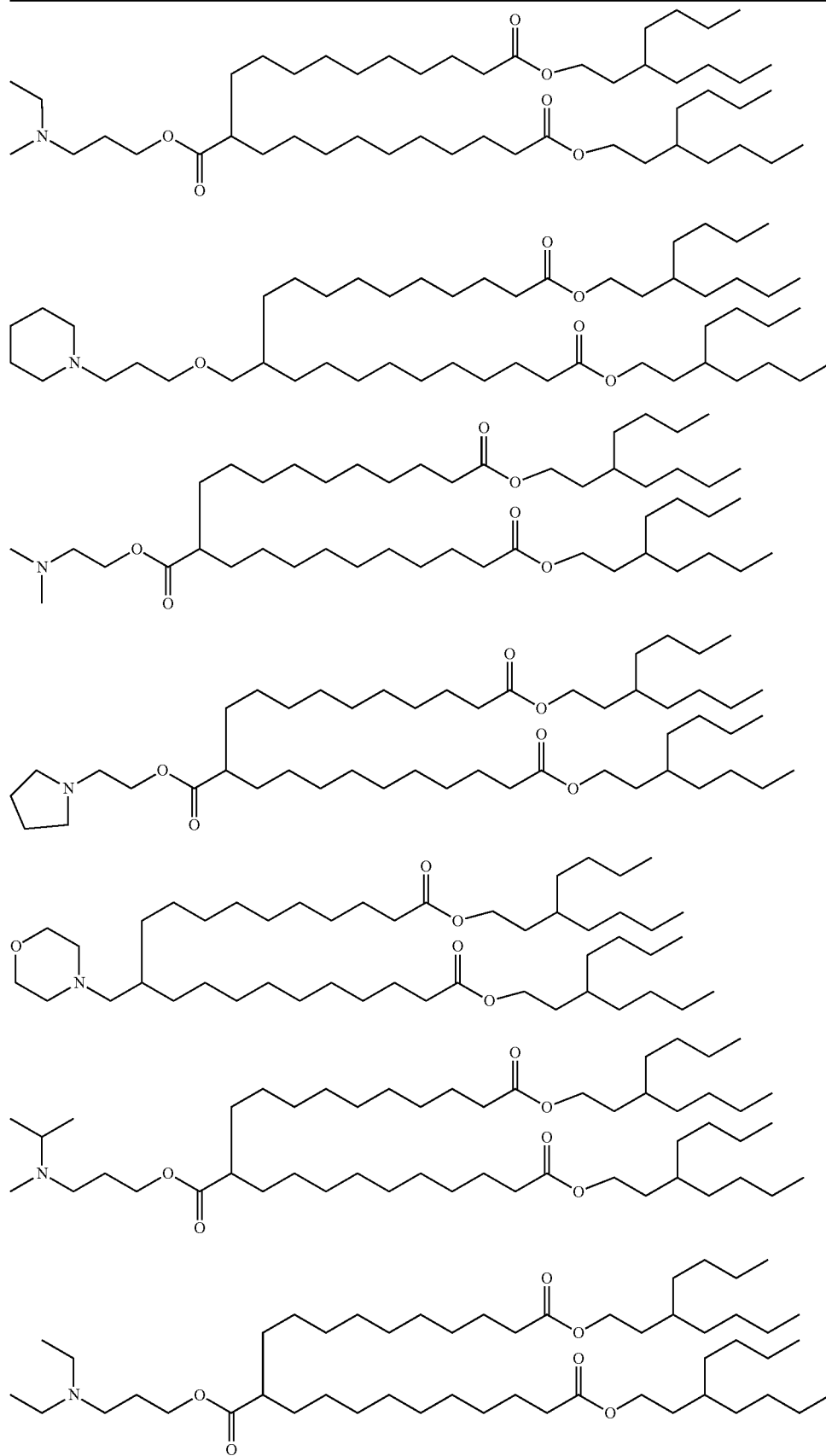


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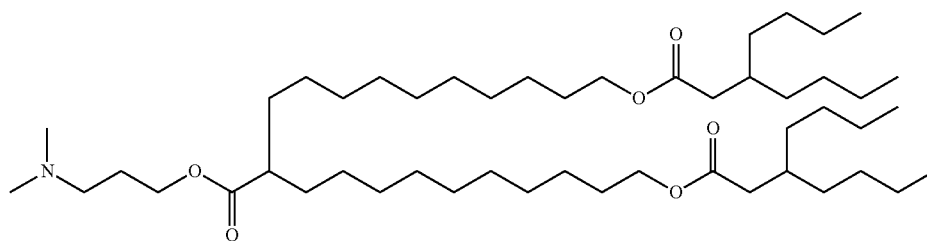
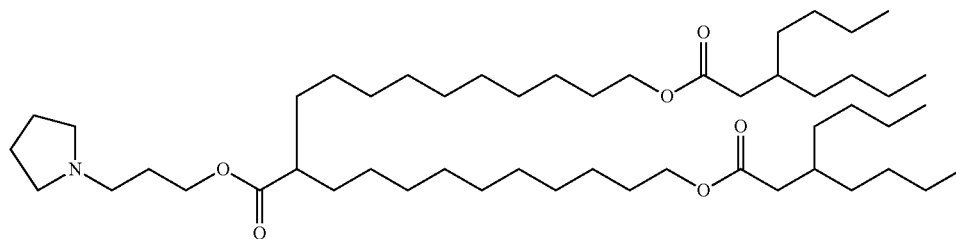
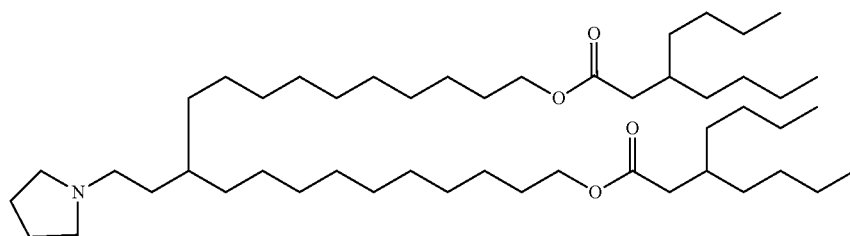
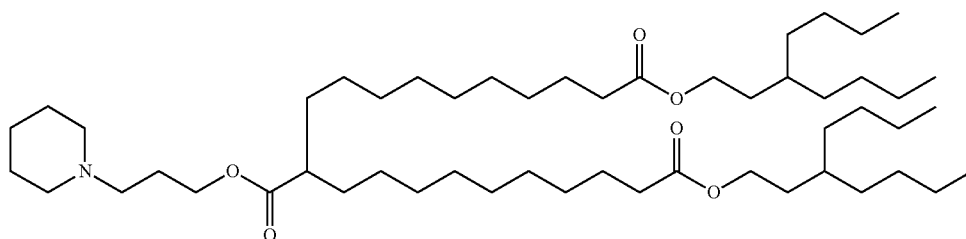
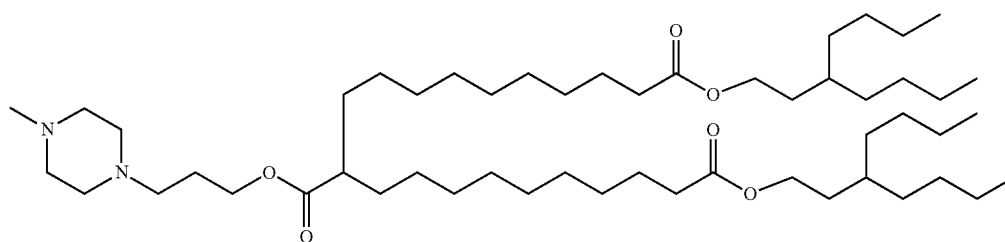
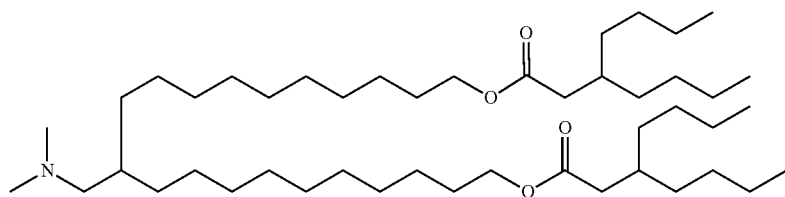


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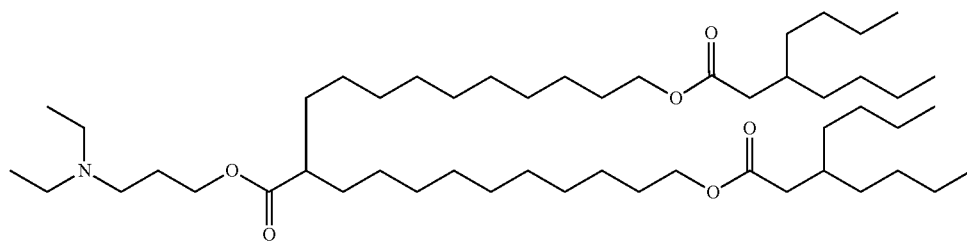
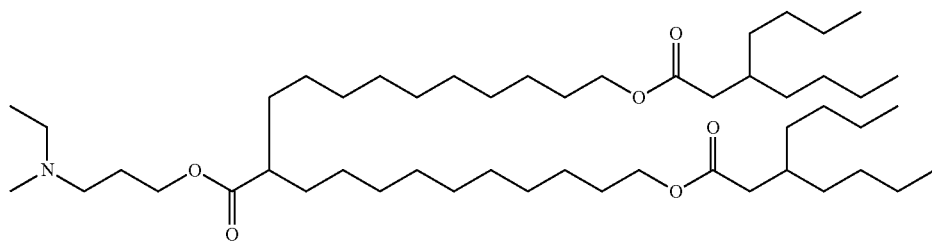
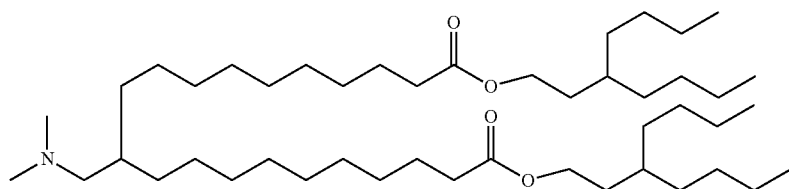
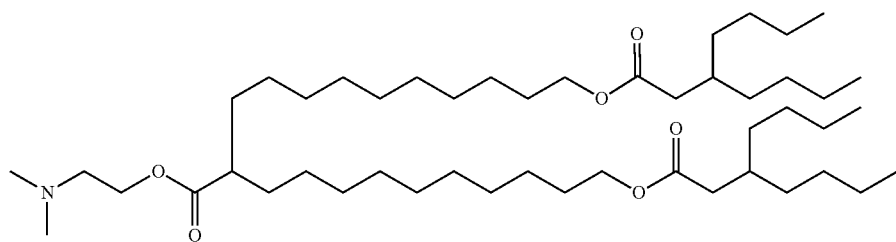
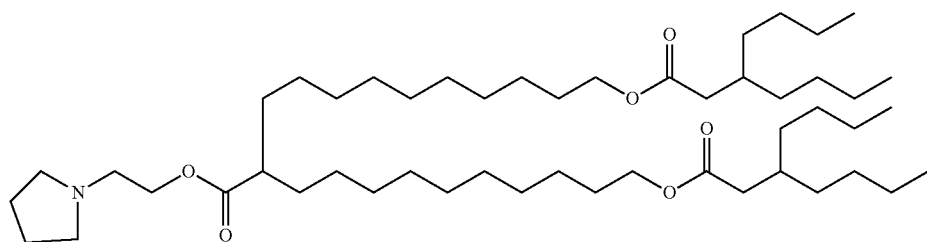
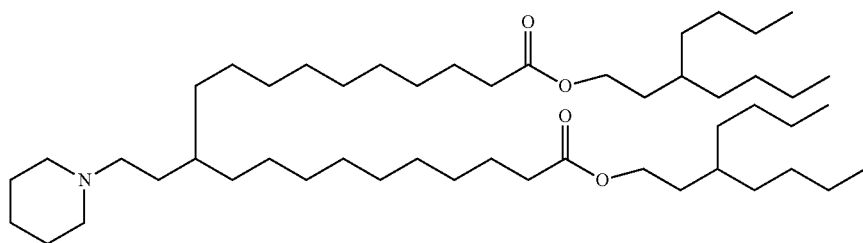


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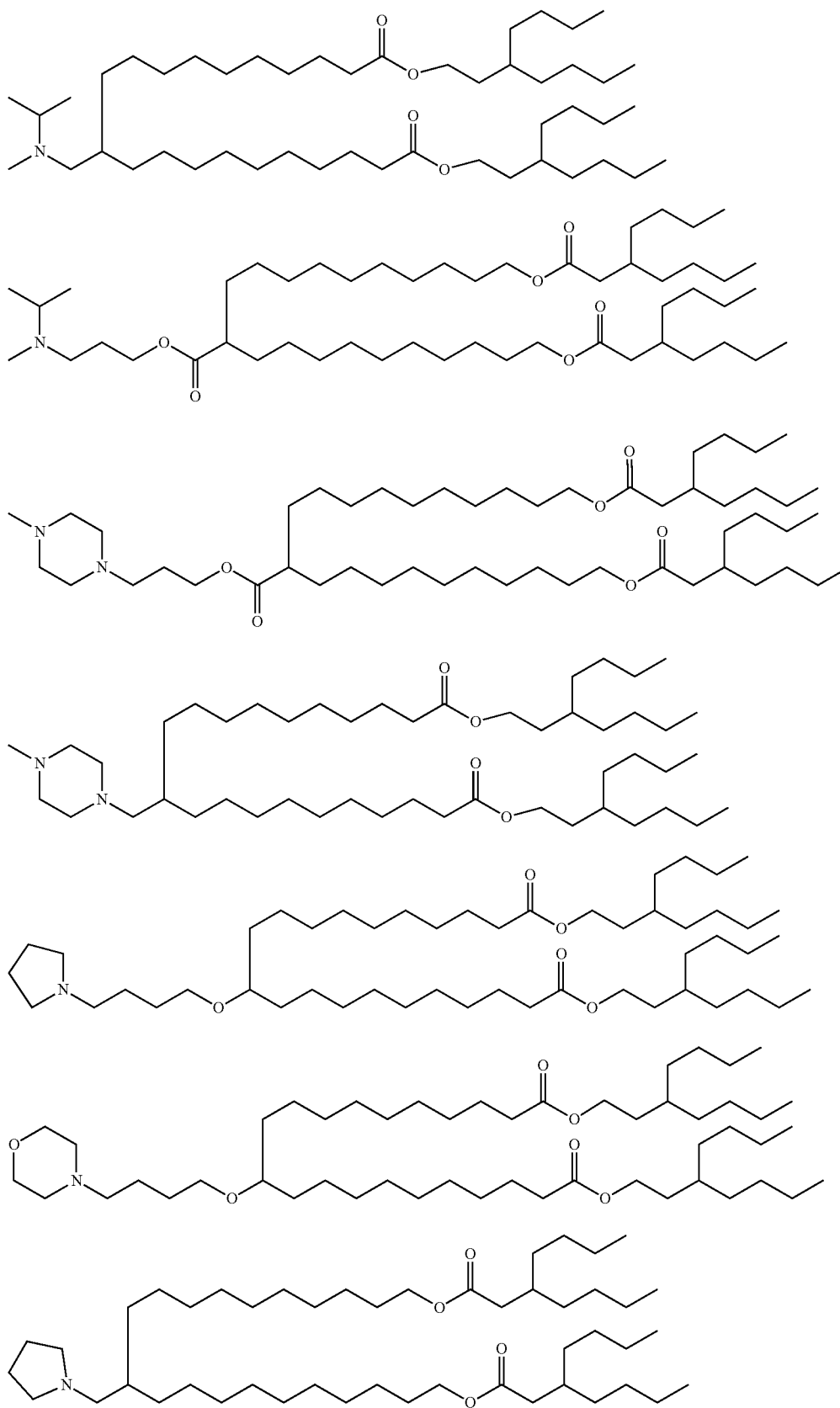


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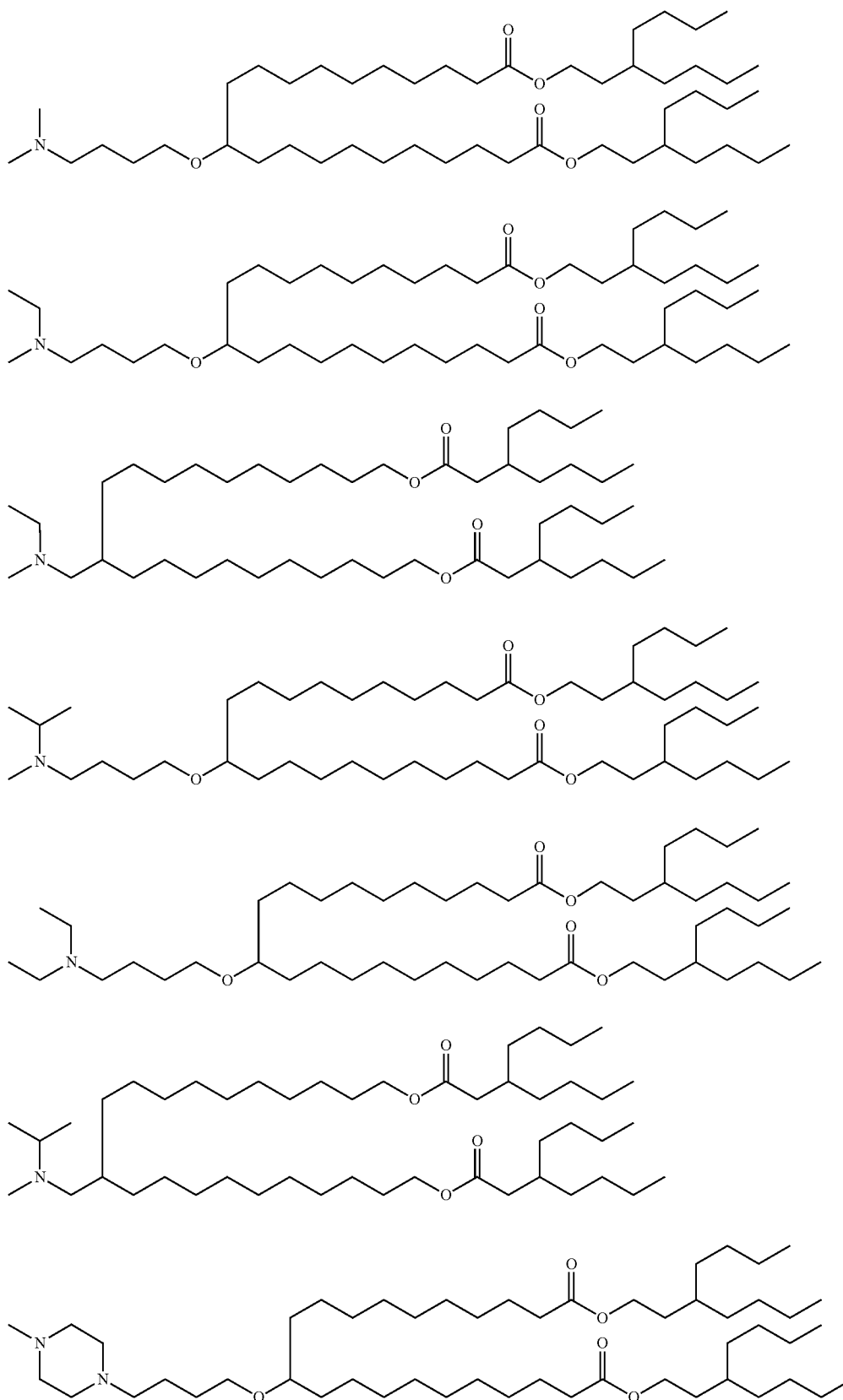


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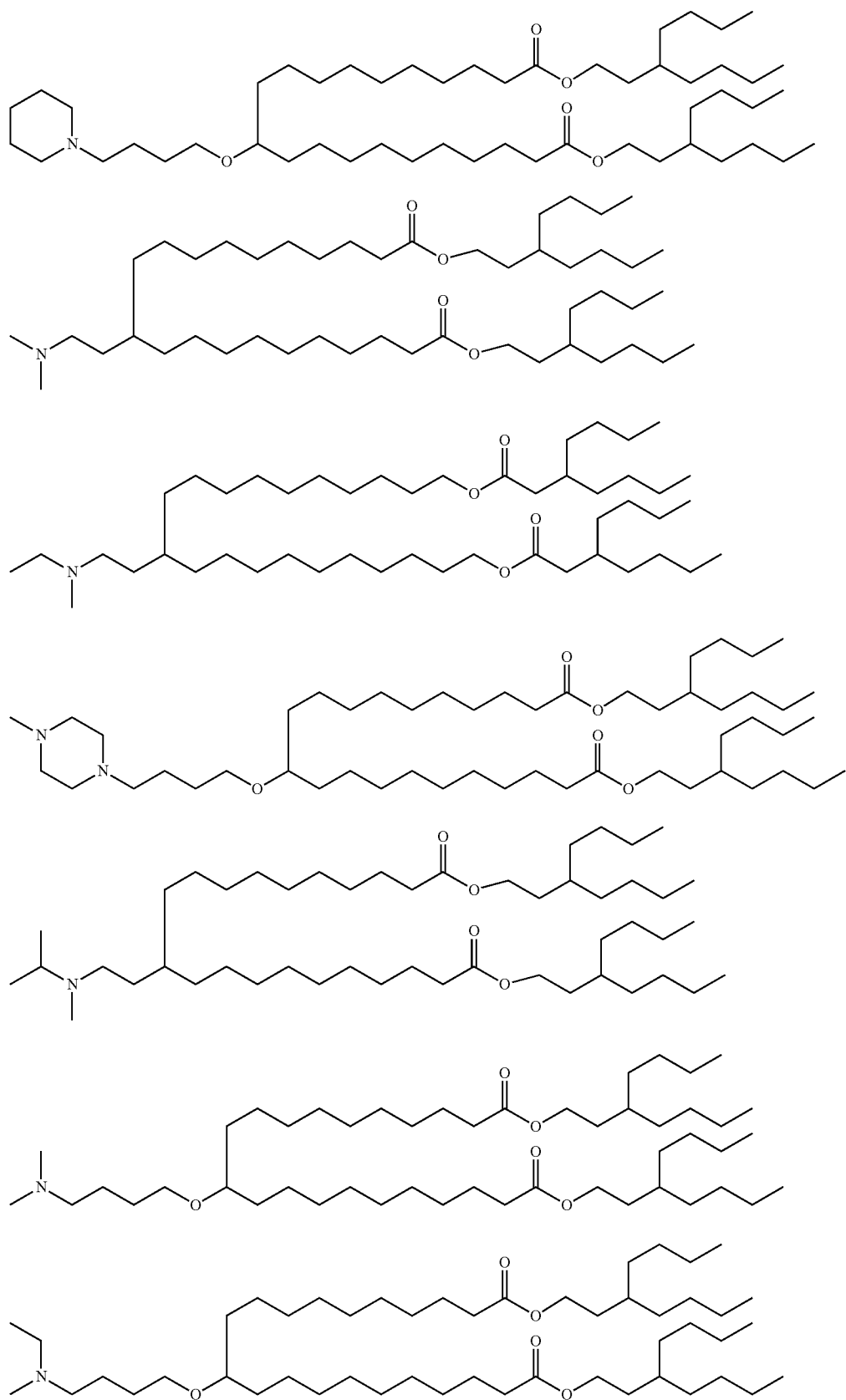


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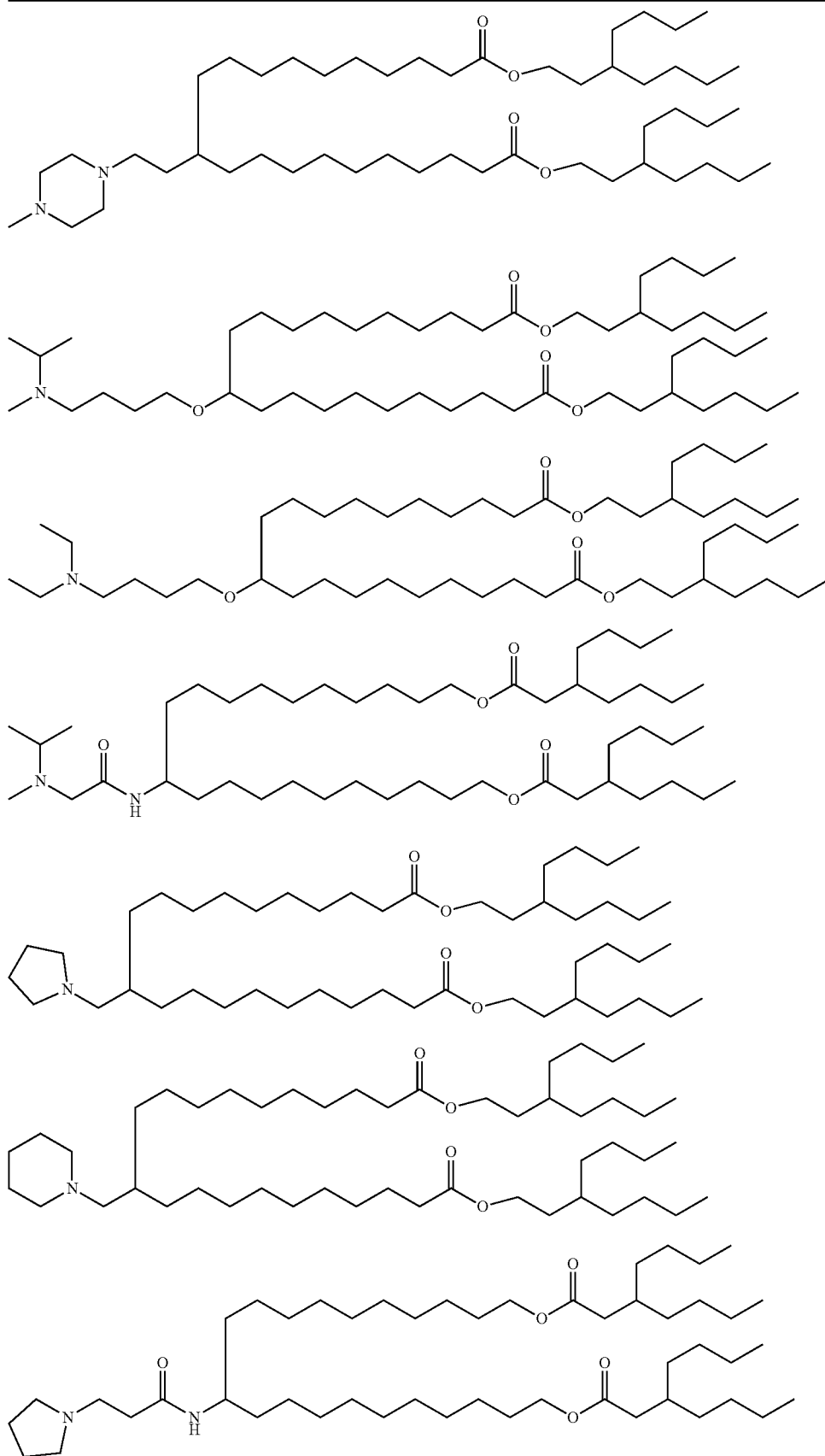


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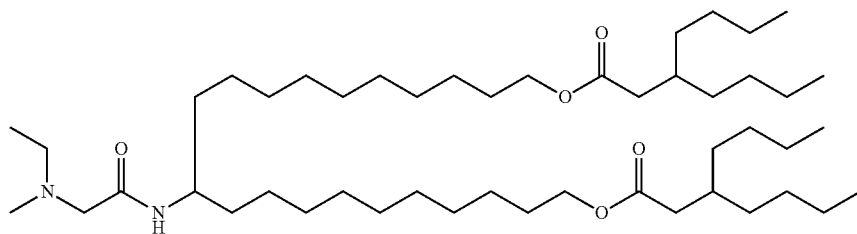
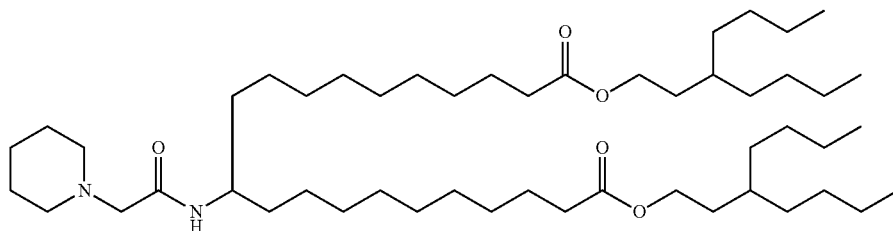
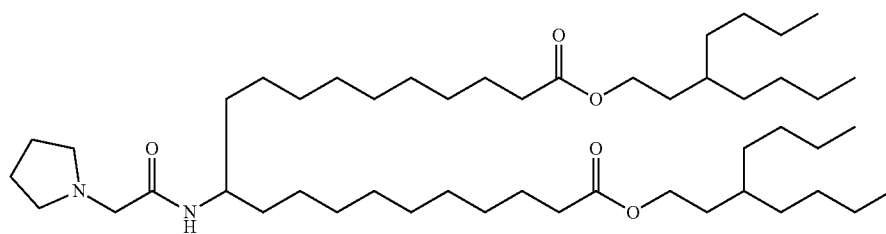
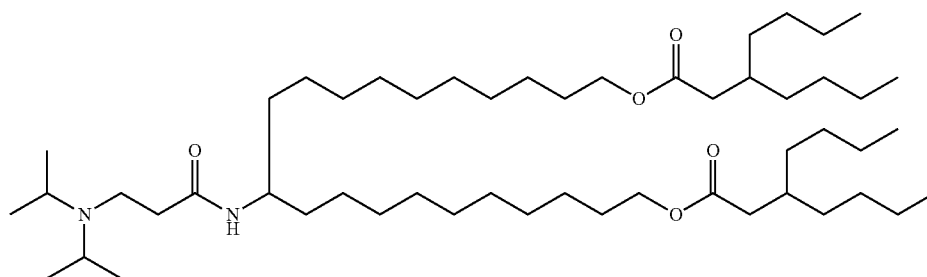
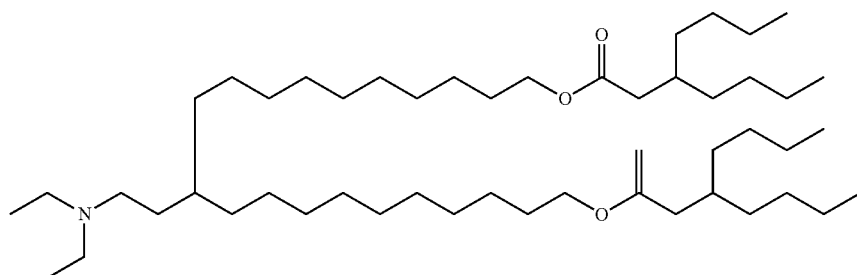
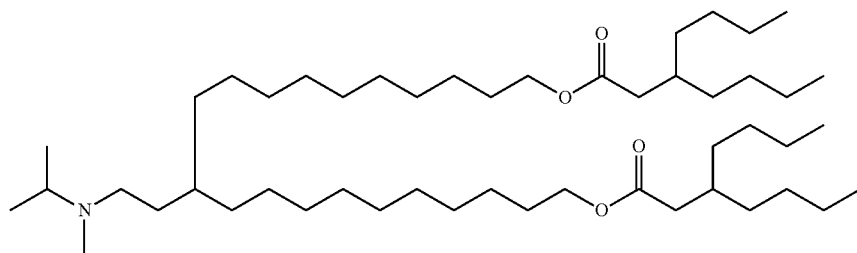


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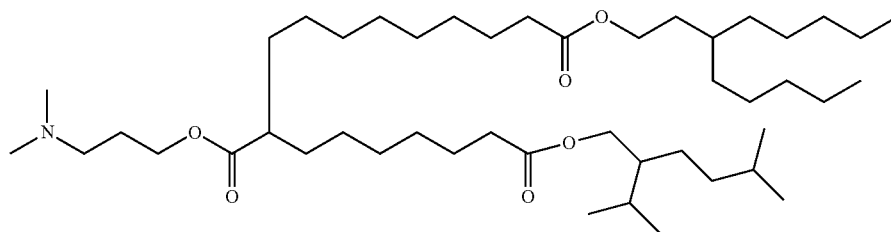
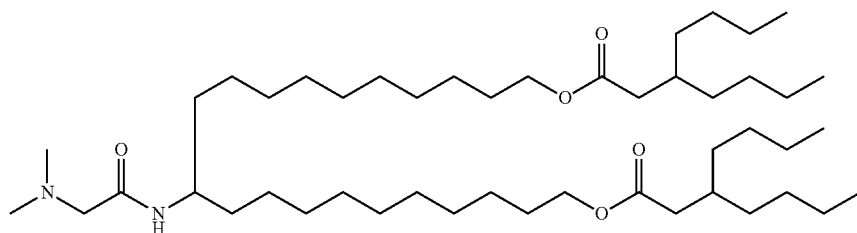
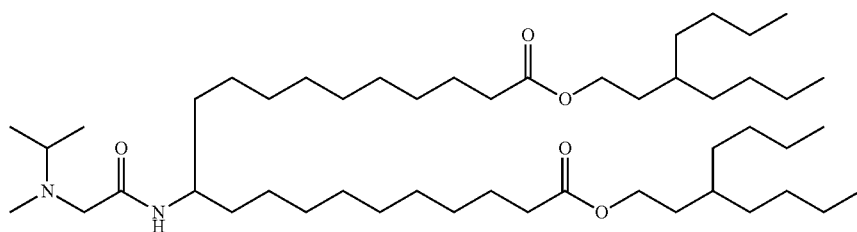
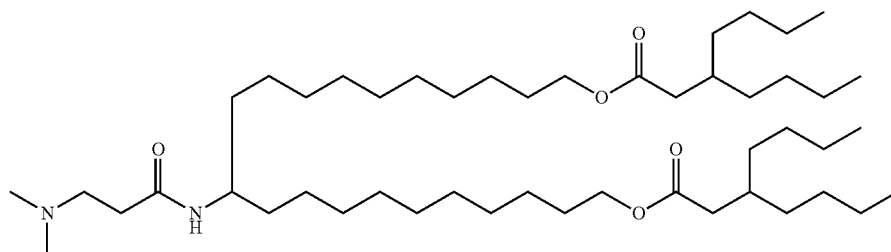
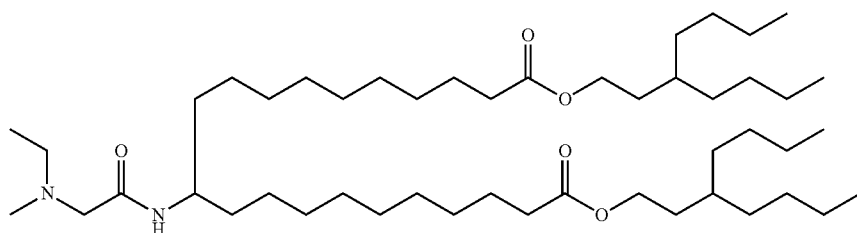
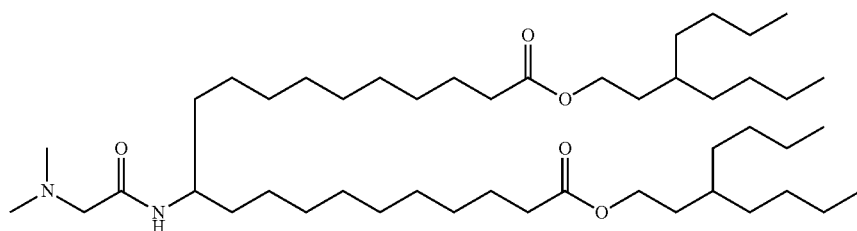


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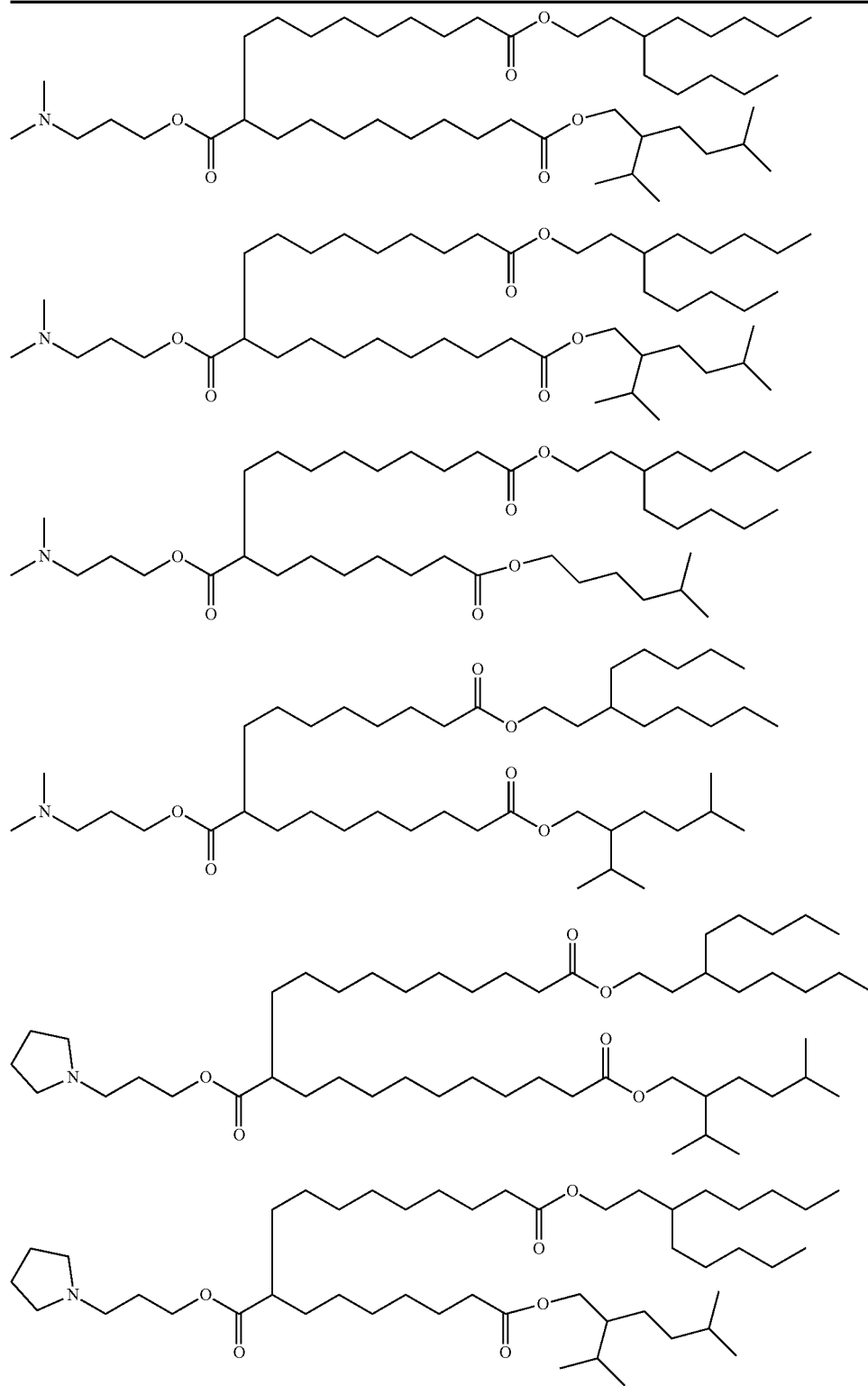


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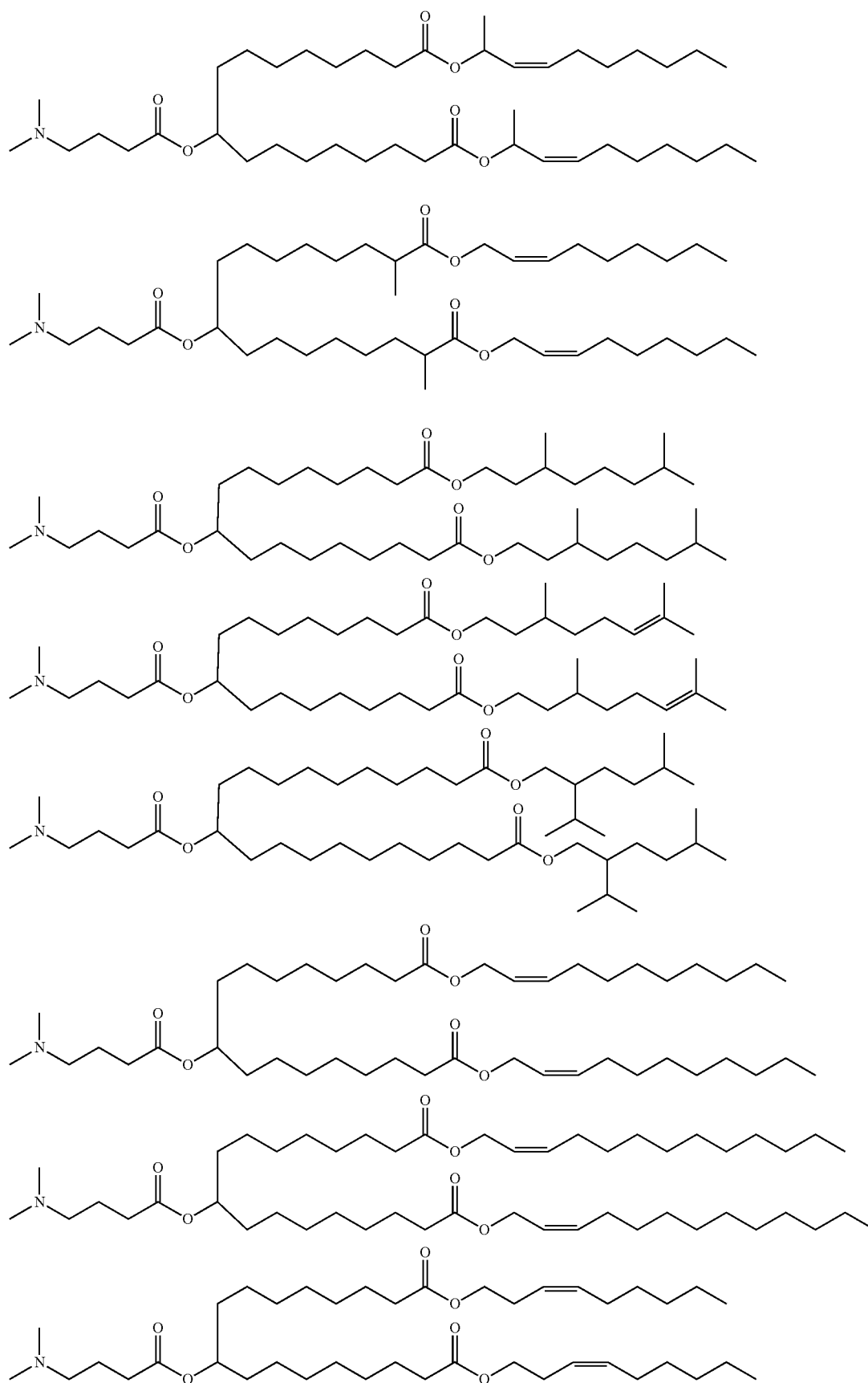
In another aspect, the present invention relates to a method of preparing a compound of Formula I-VII. Suitable exemplary synthetic methods are illustrated in Schemes 1-27 shown in the Examples section below.

In one embodiment, the cationic lipid of the present invention is selected from the following compounds, and salts thereof (including pharmaceutically acceptable salts thereof). These cationic lipids are suitable for forming nucleic acid-lipid particles.

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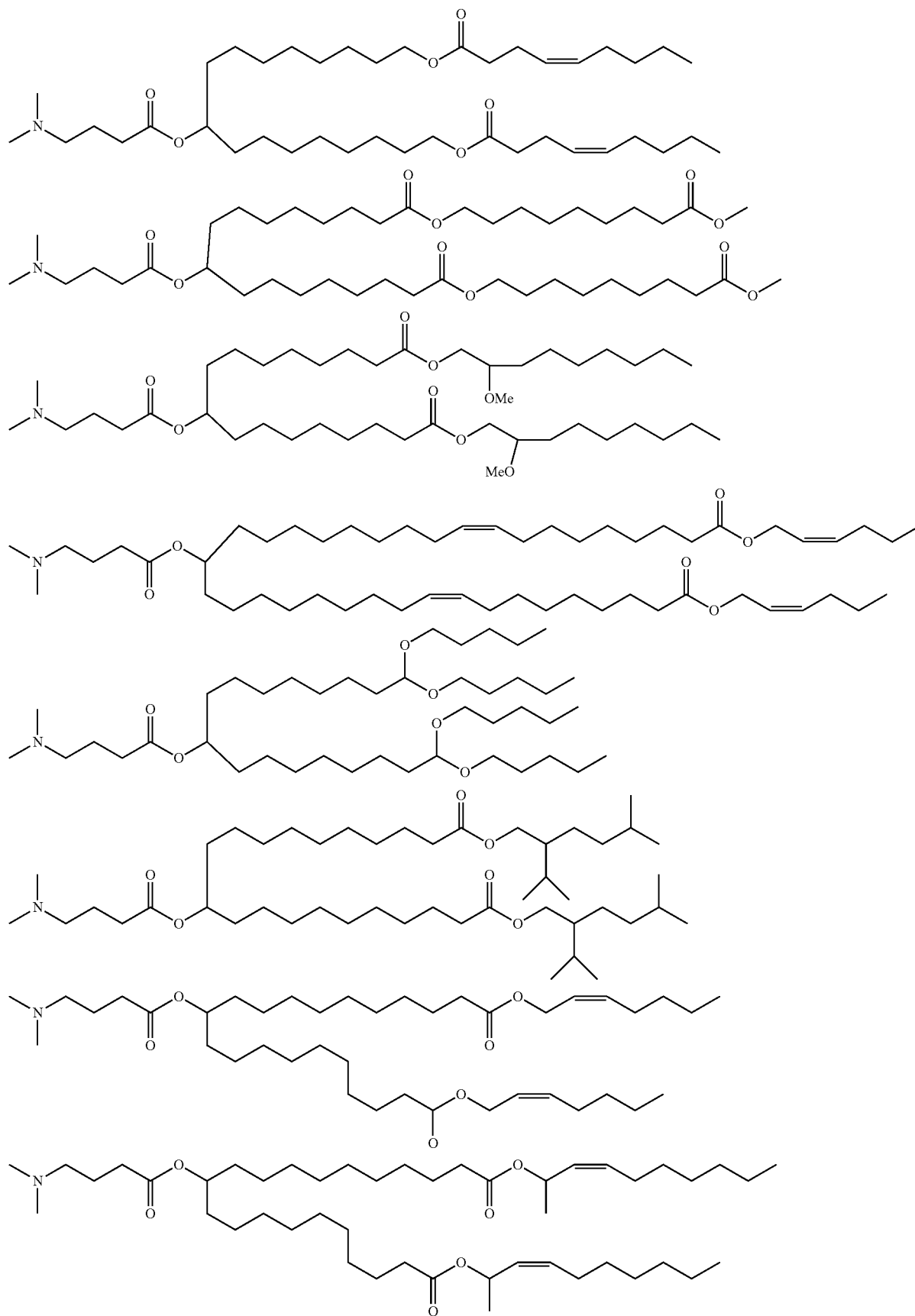


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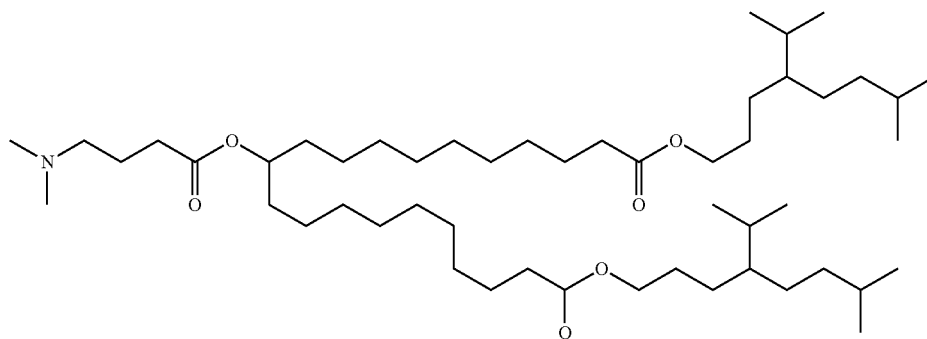
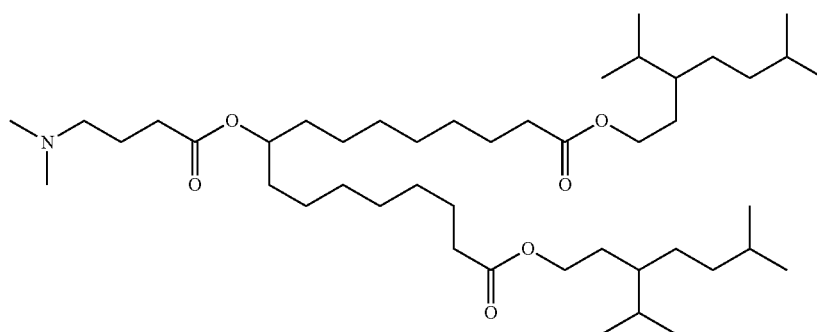
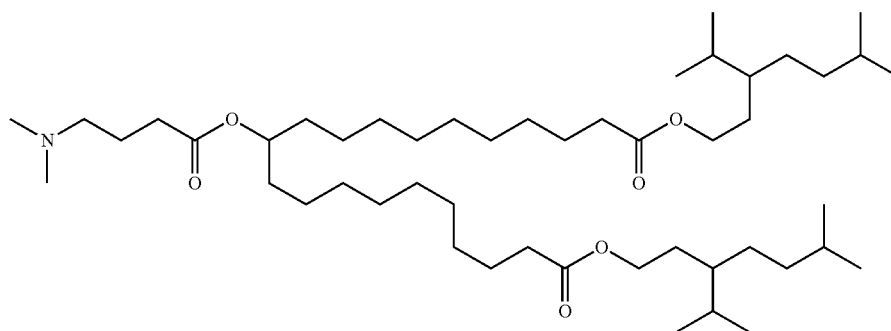
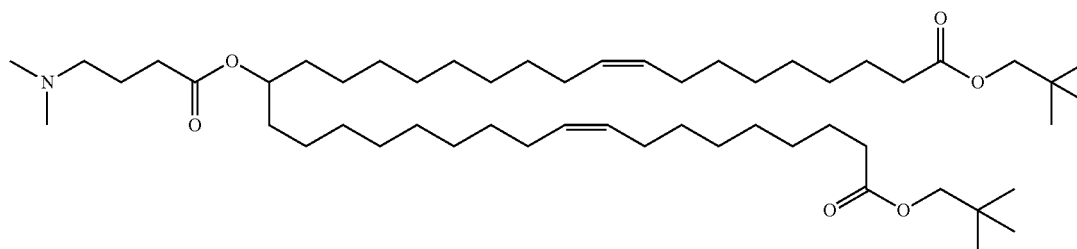
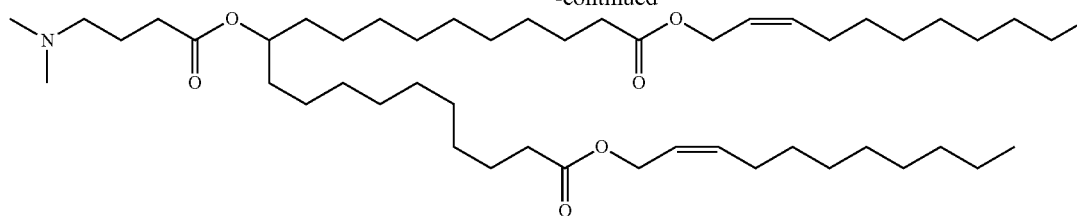


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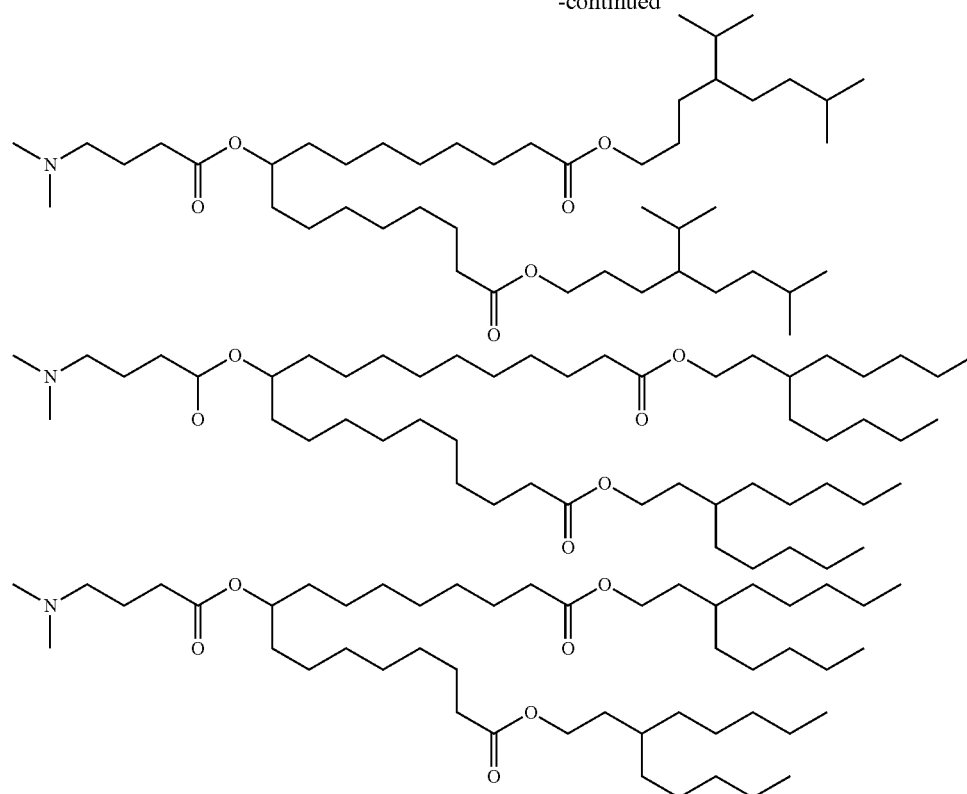


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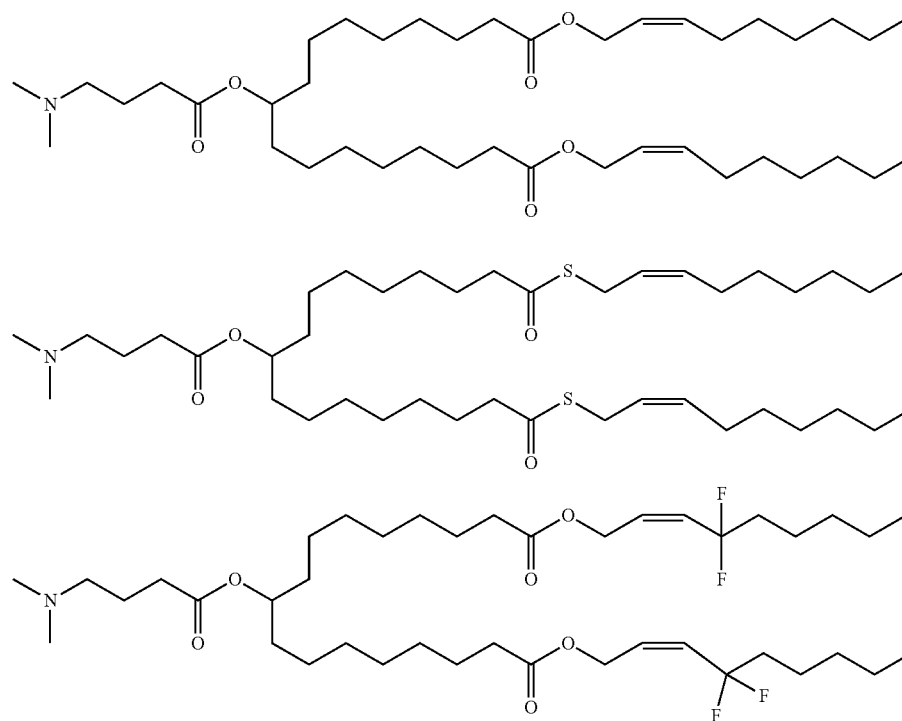
341

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In another embodiment, the cationic lipid of the present invention is selected from the following compounds, and salts thereof (including pharmaceutically acceptable salts thereof):

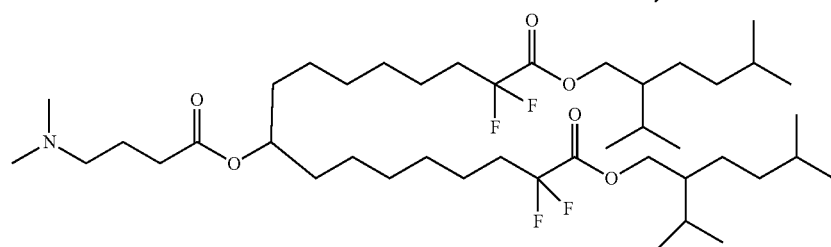
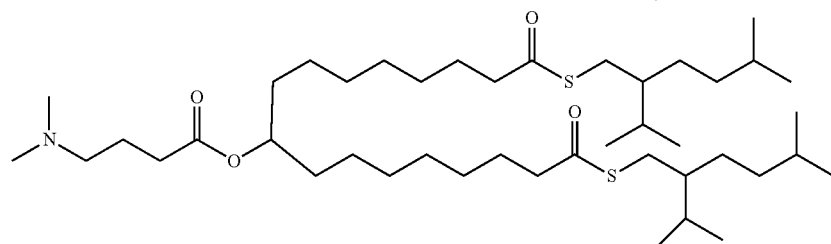
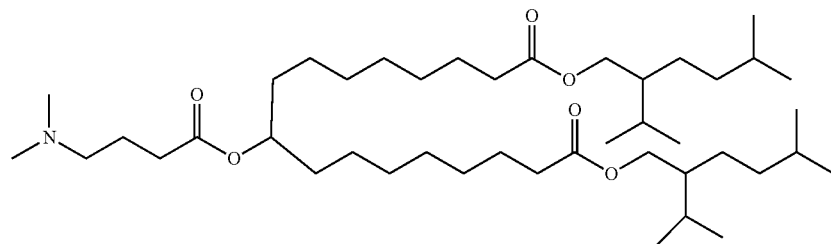
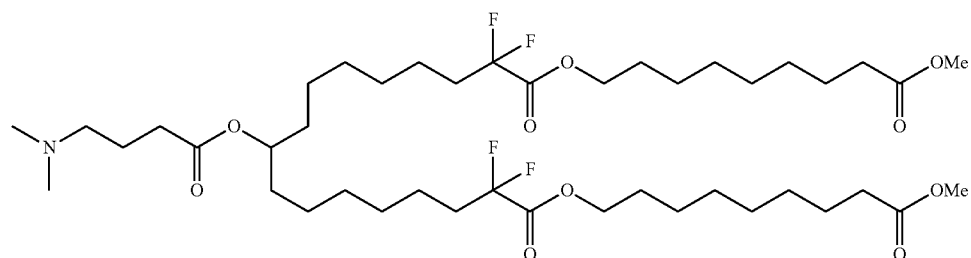
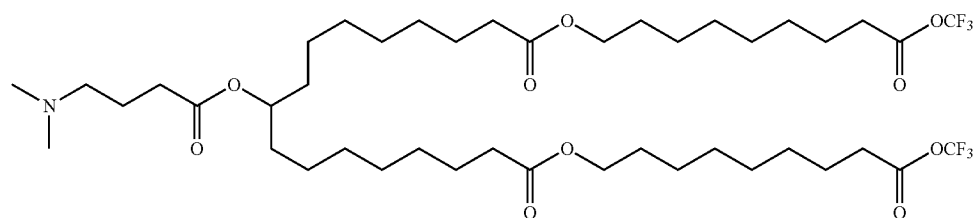
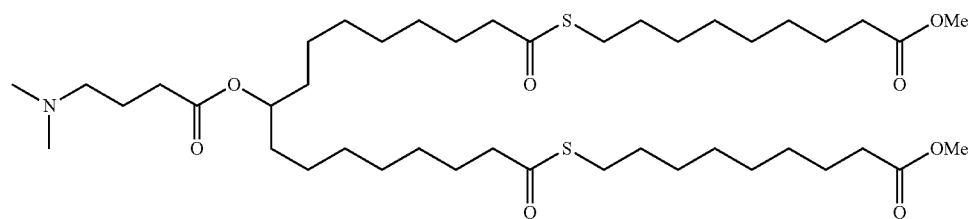
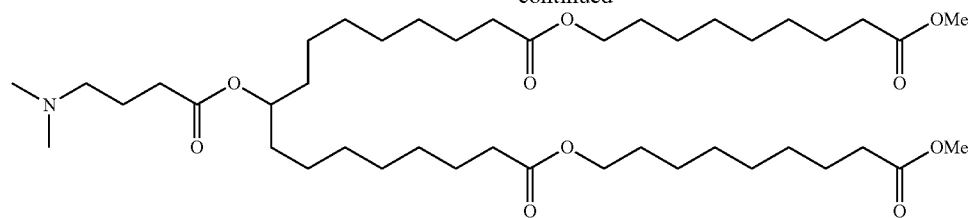


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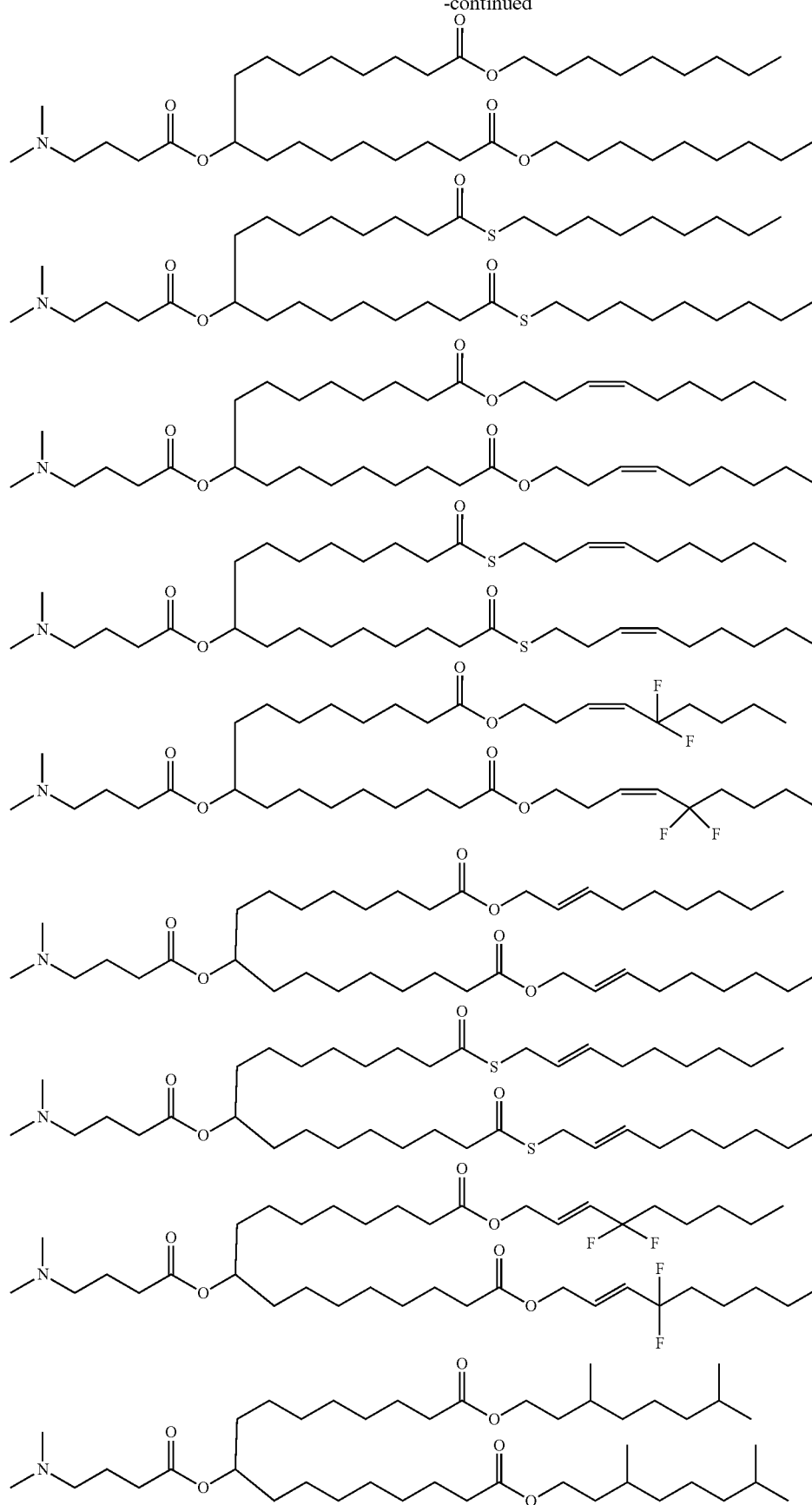


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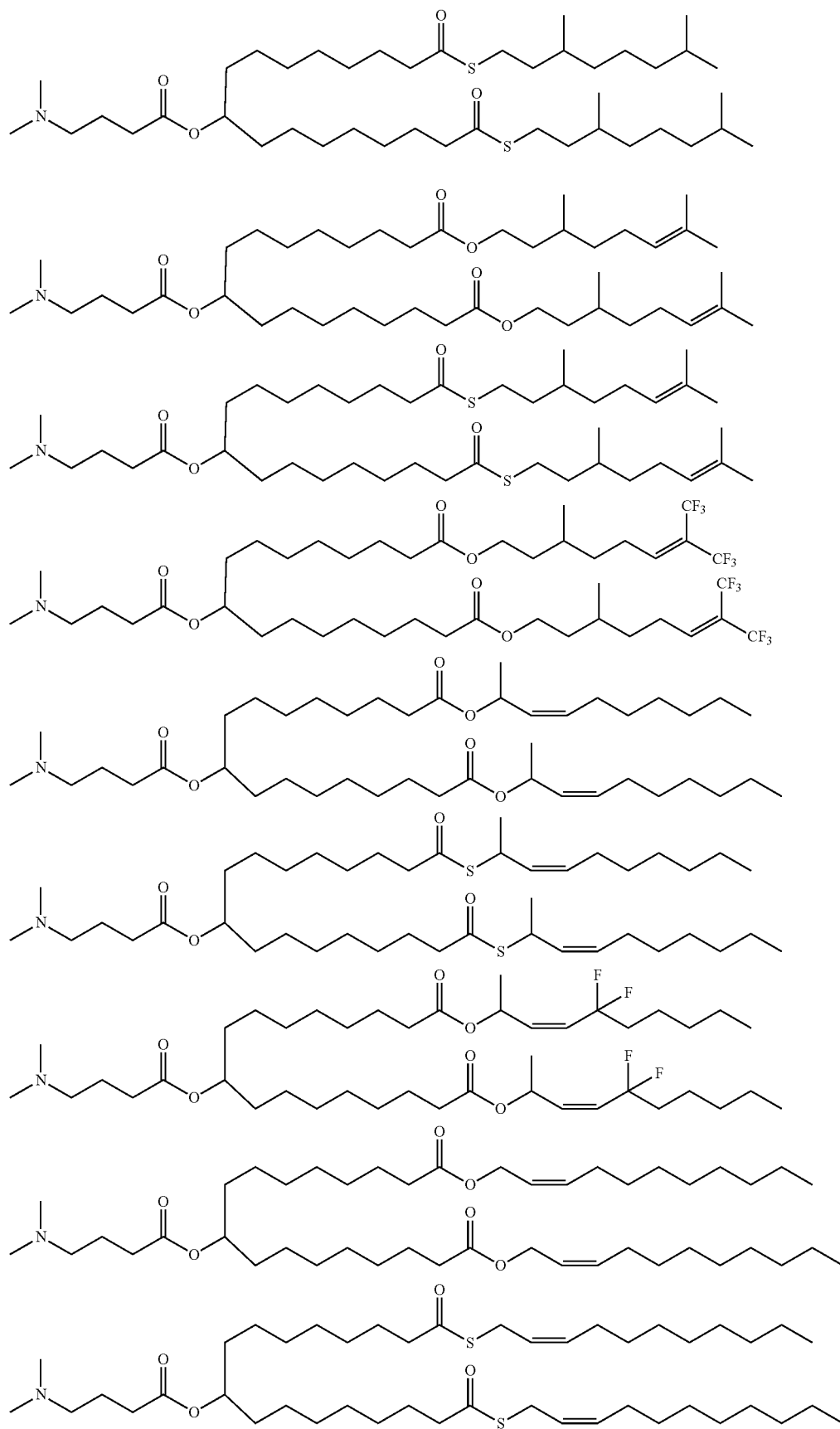


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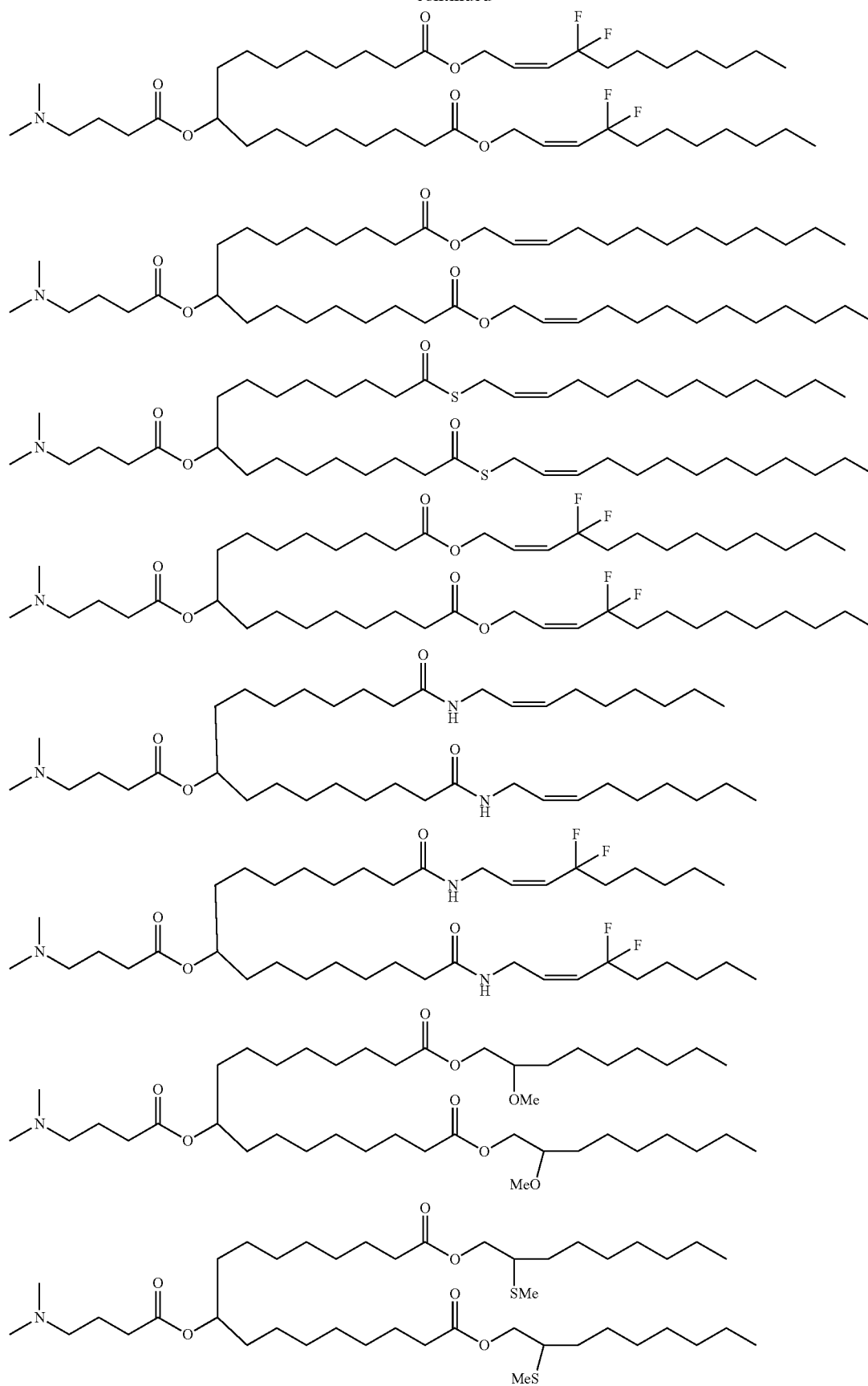


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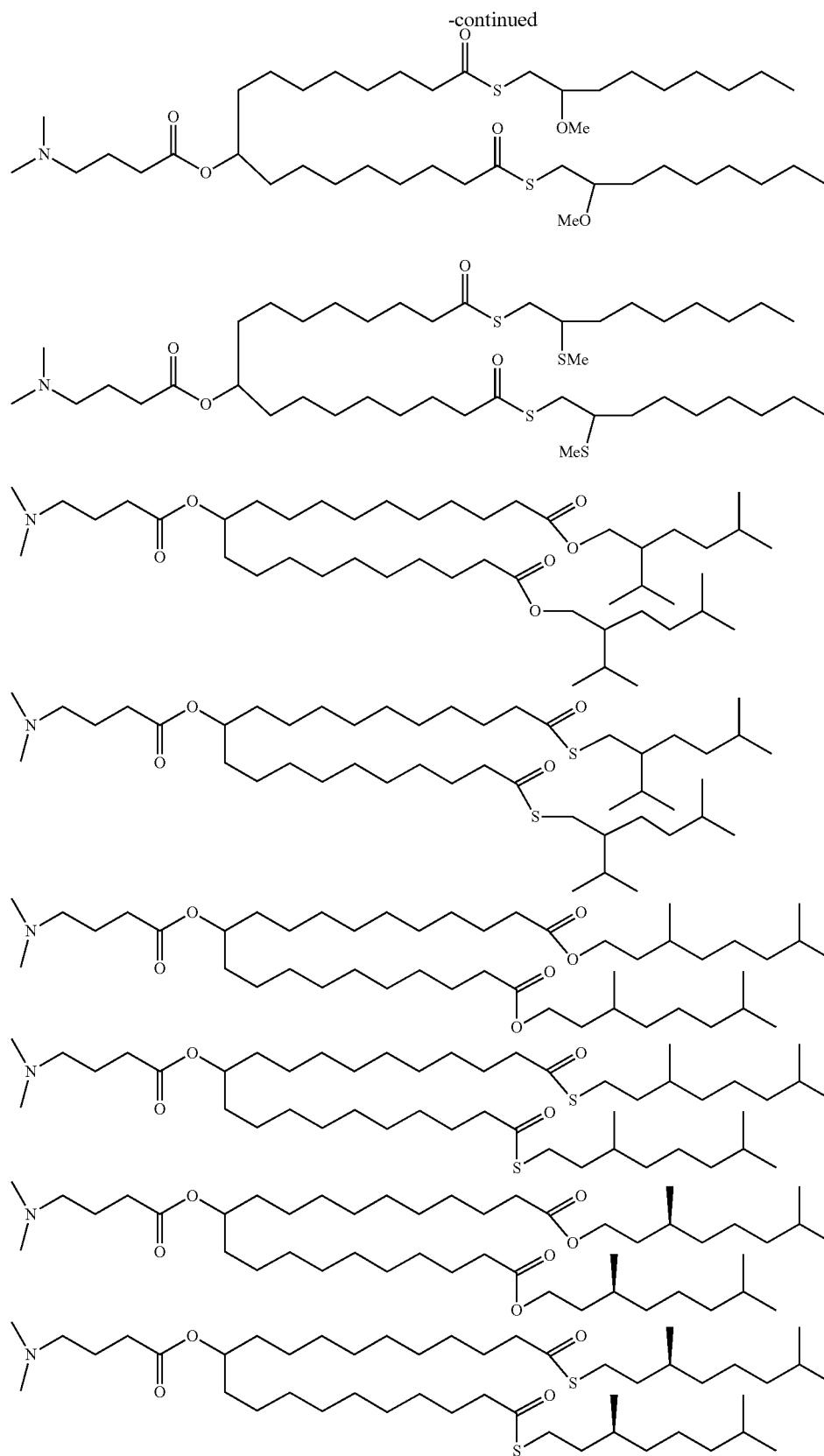
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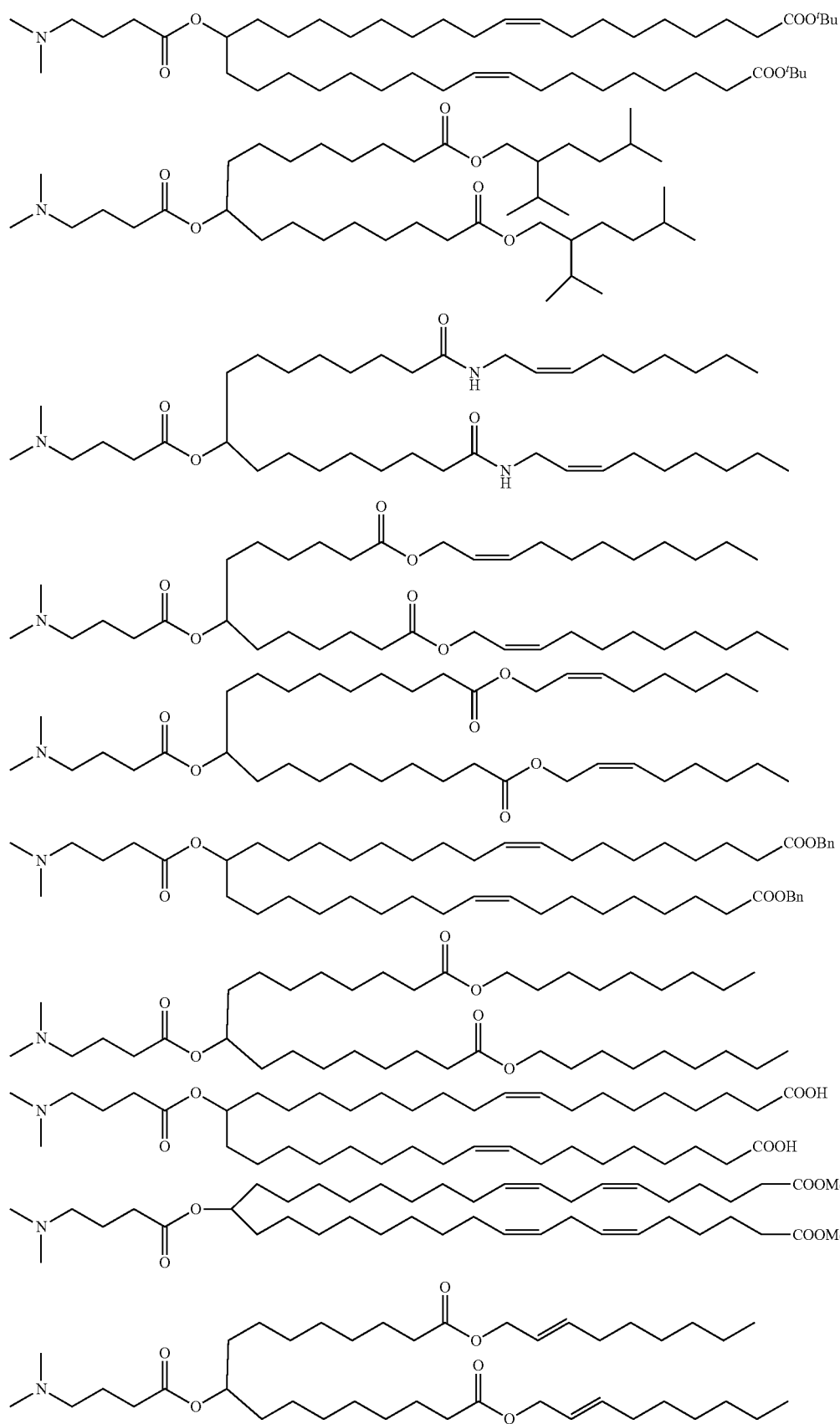
In another embodiment, the cationic lipid of the present invention is selected from the following compounds, and

salts thereof (including pharmaceutically acceptable salts thereof):

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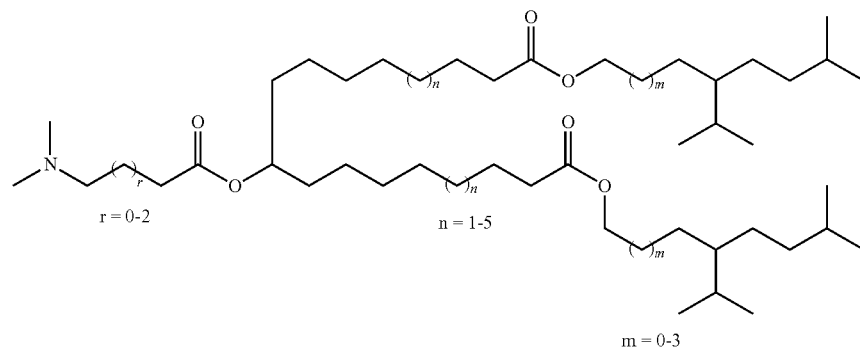
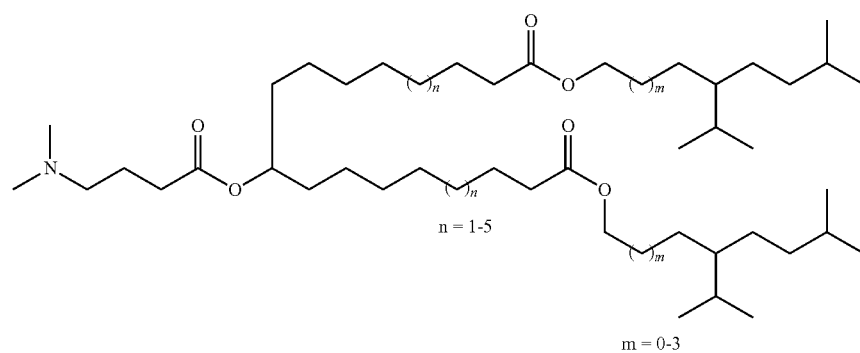
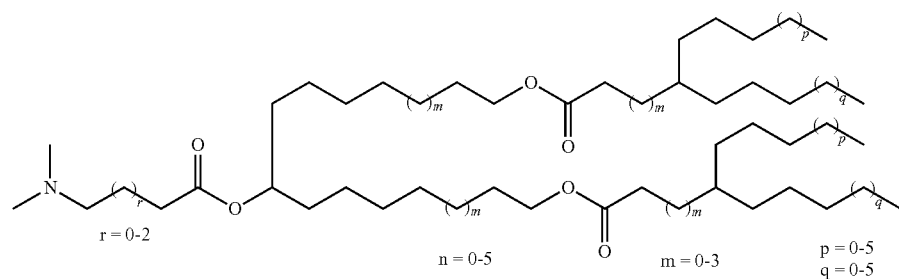
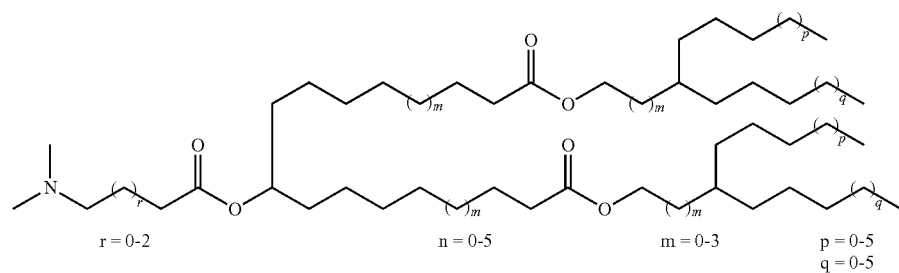
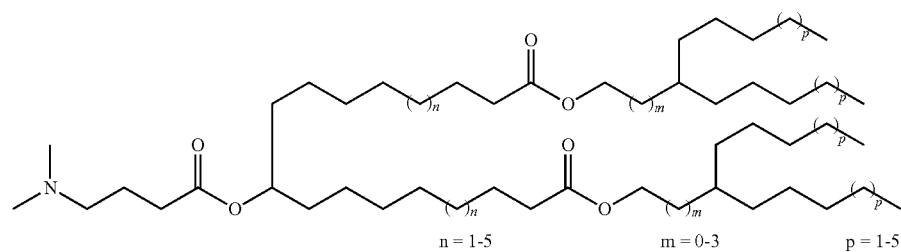


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Additional representative cationic lipids include, but are not limited to:

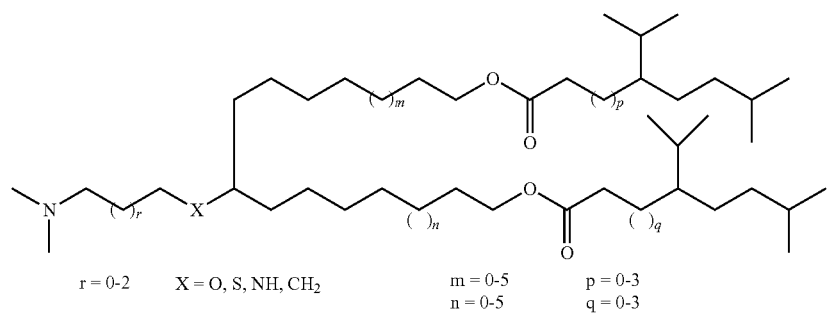
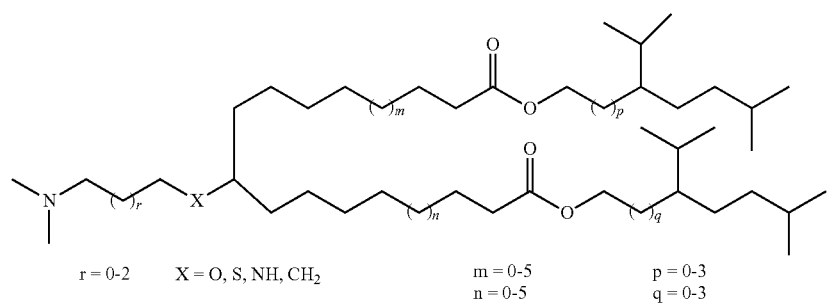
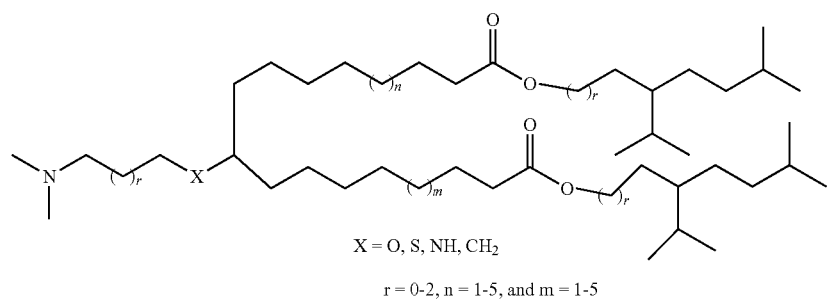
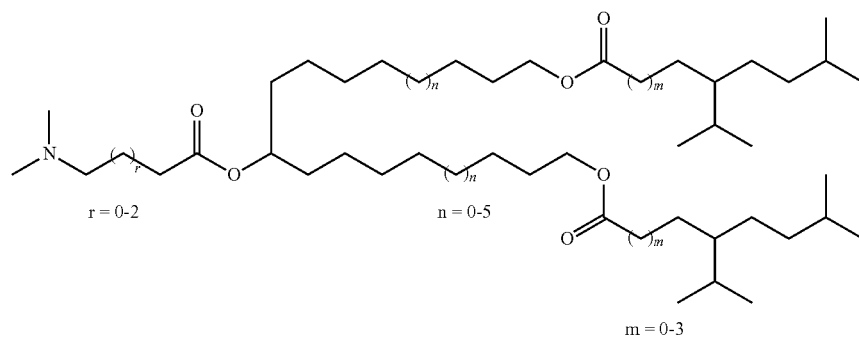
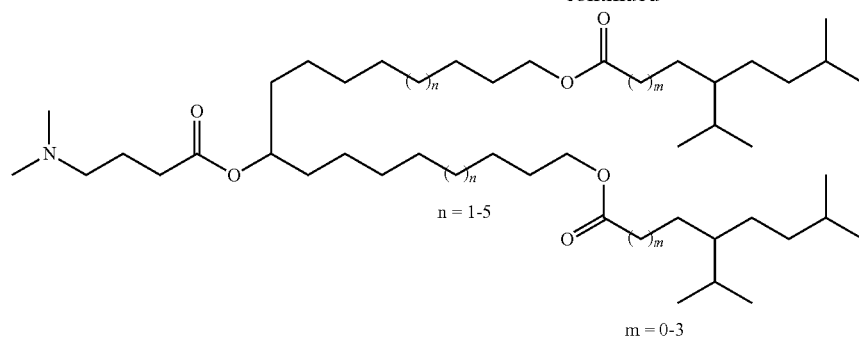


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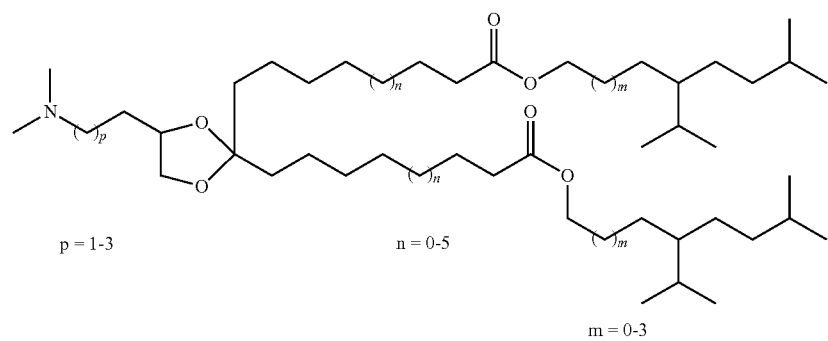
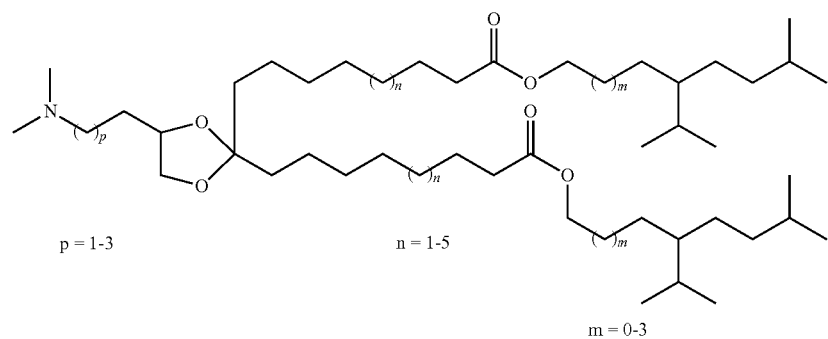
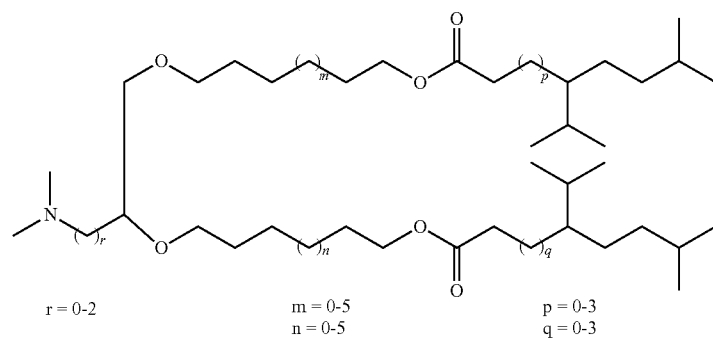
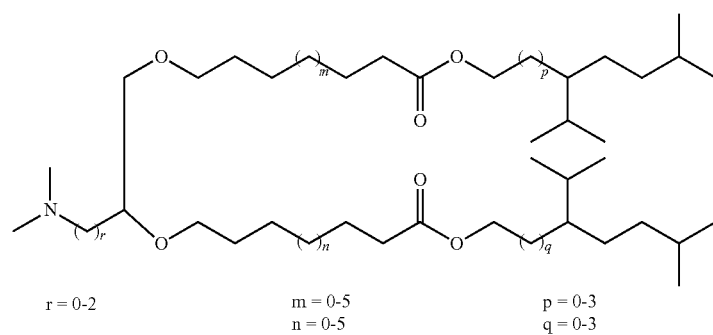
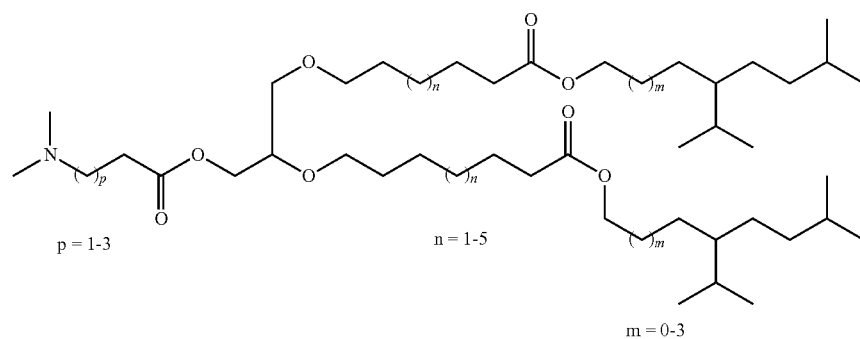


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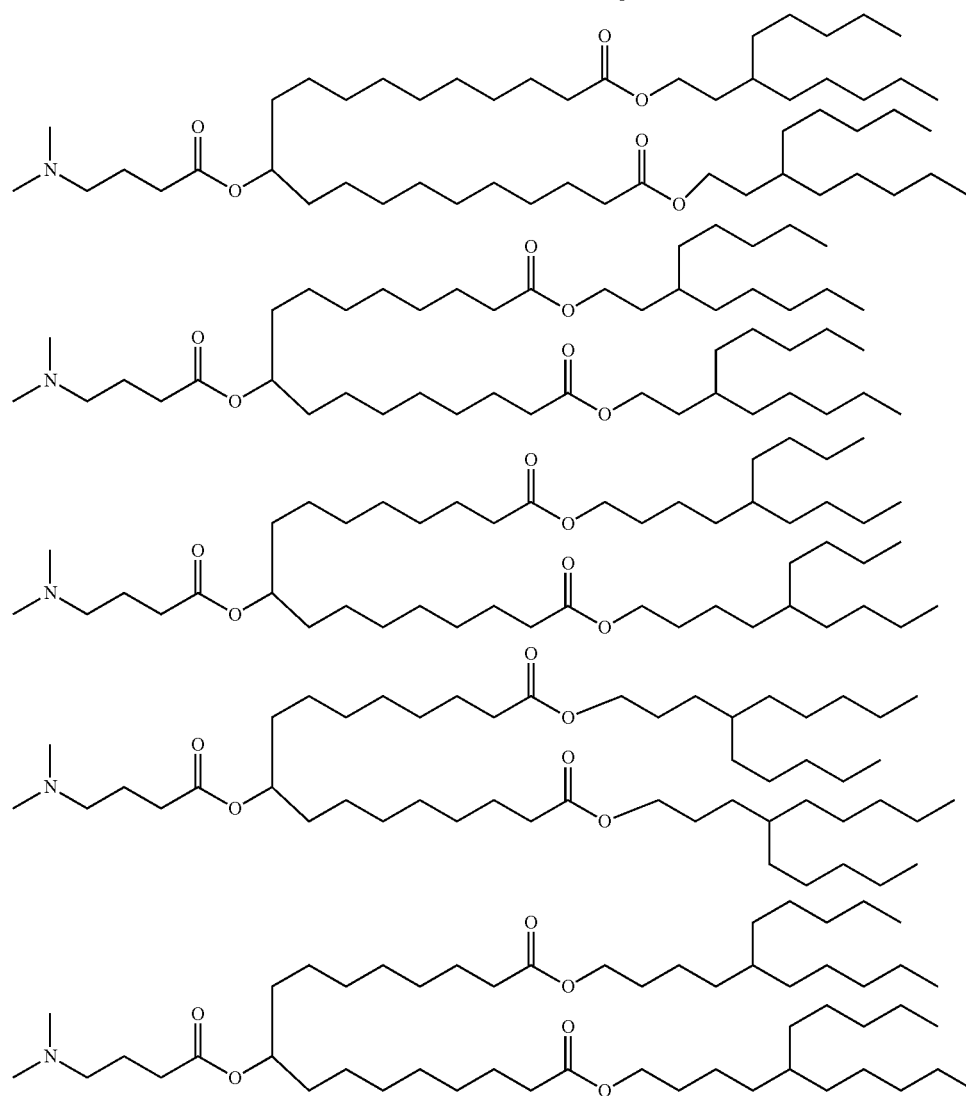
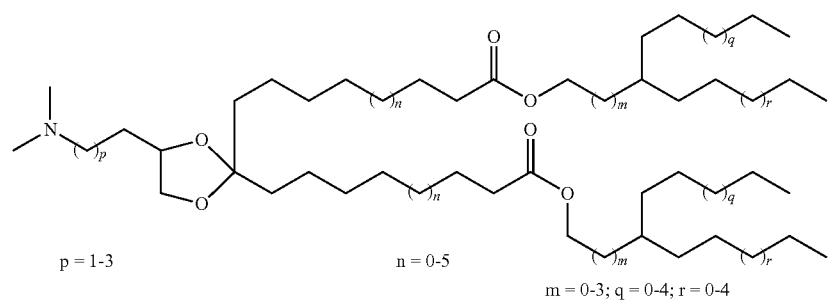
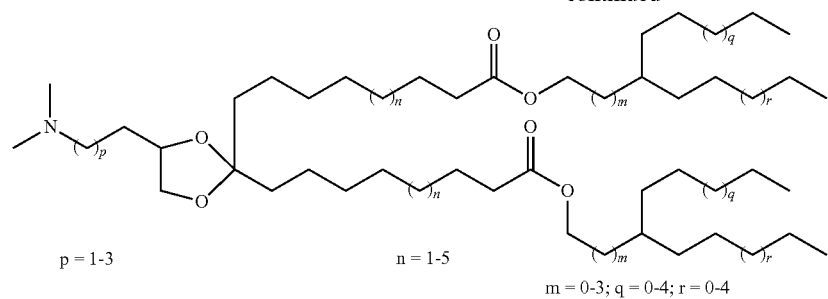


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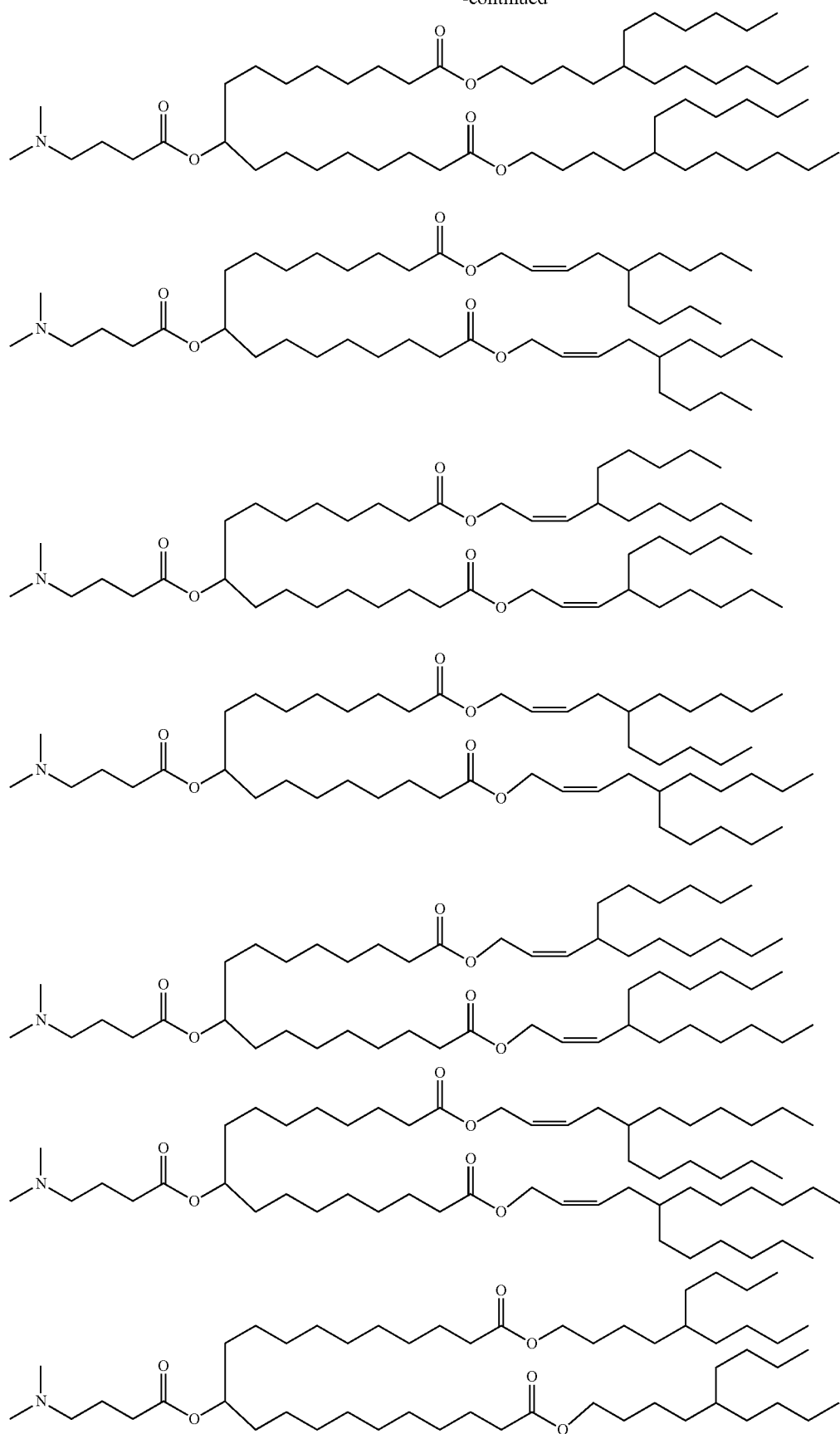


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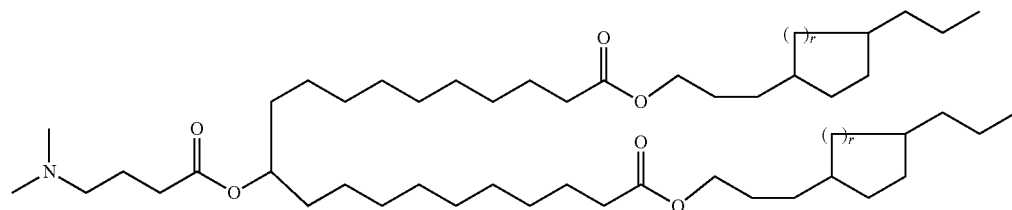
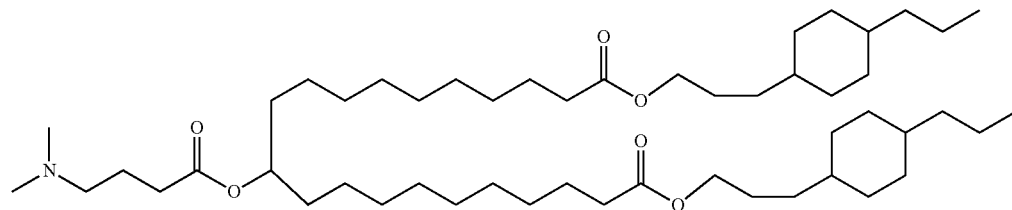
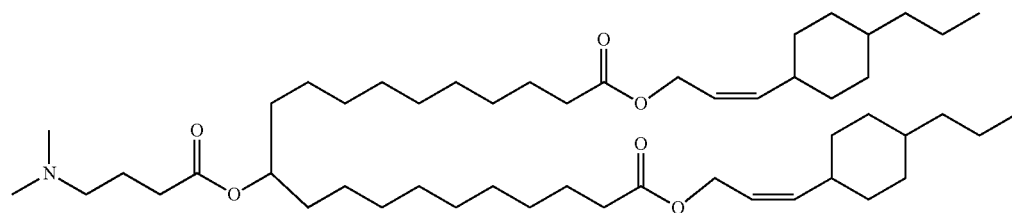
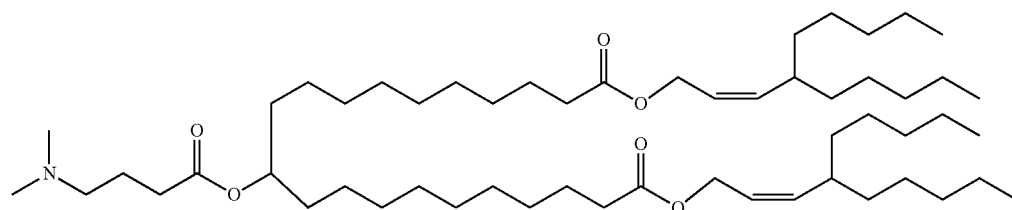
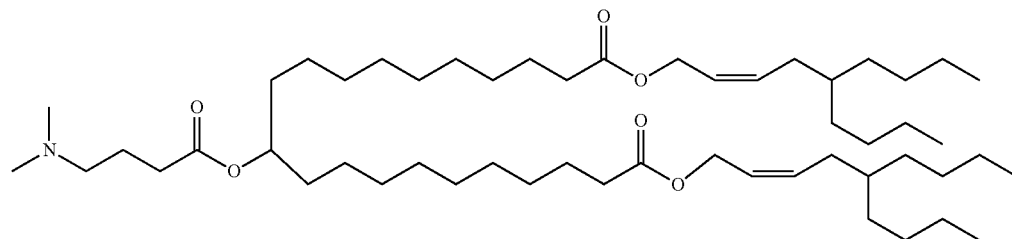
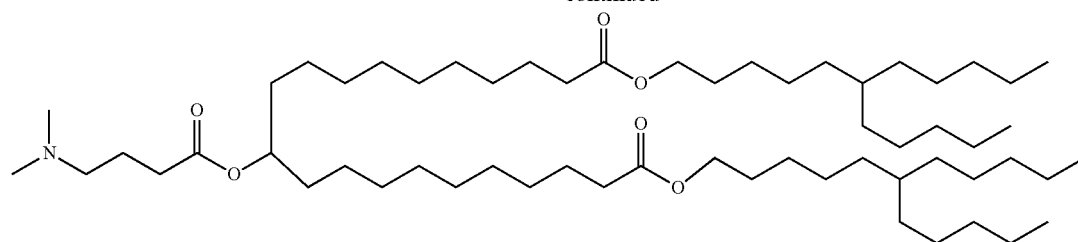


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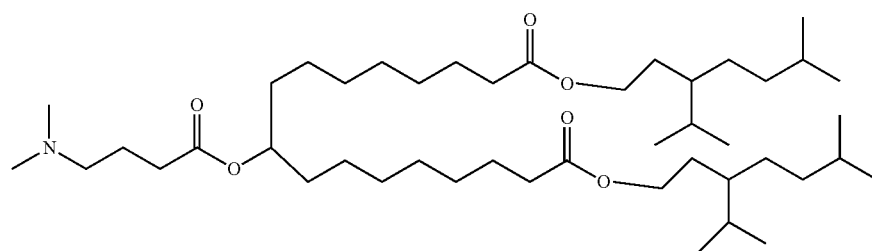
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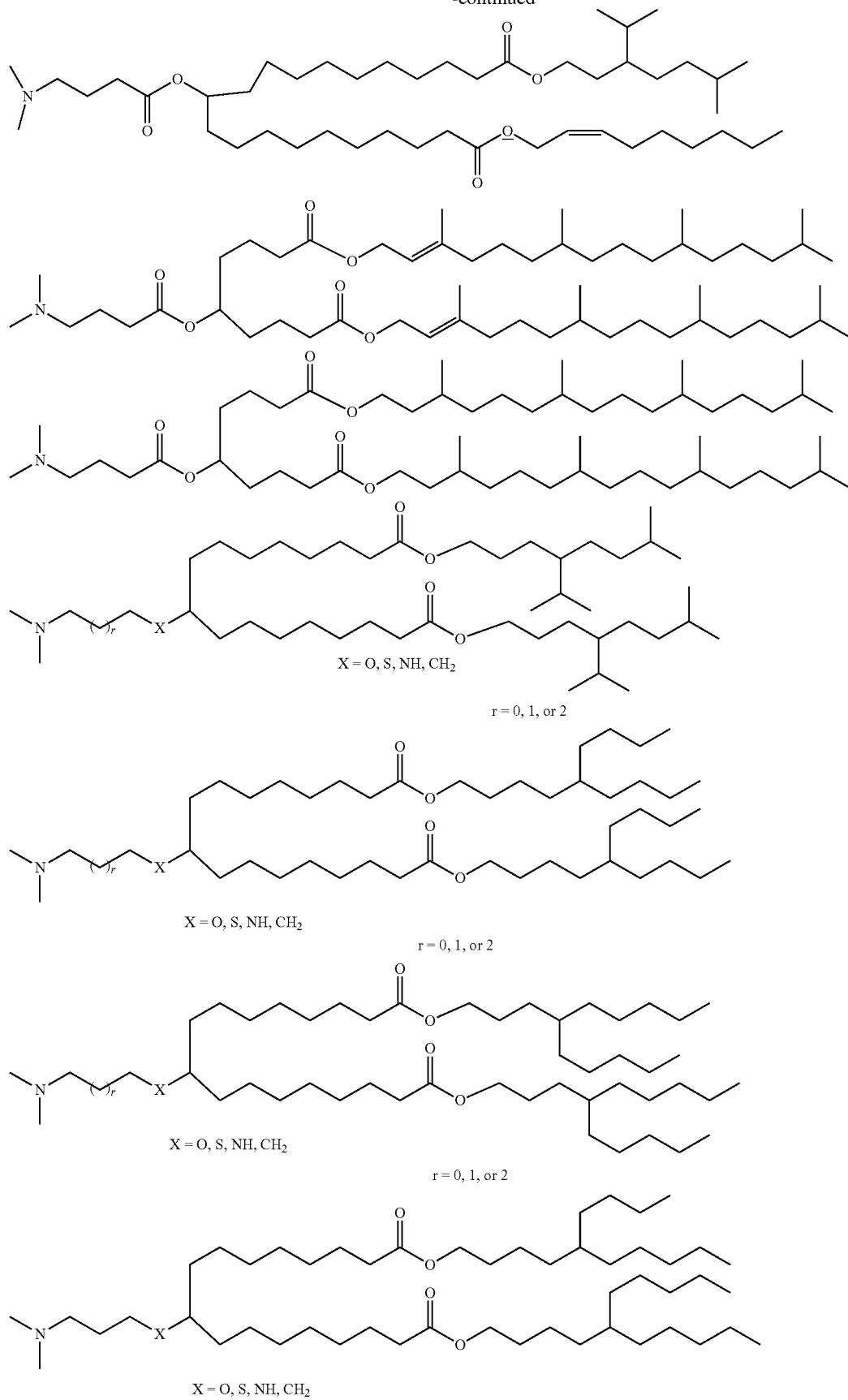


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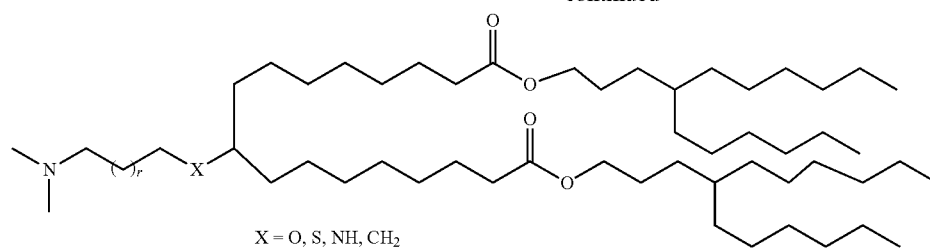


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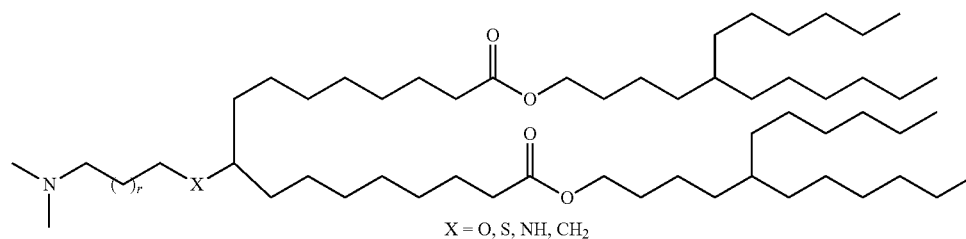
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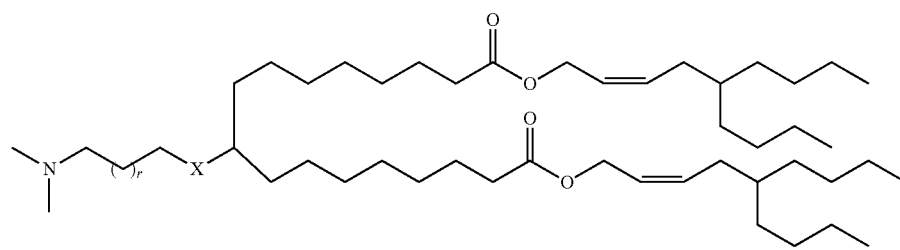
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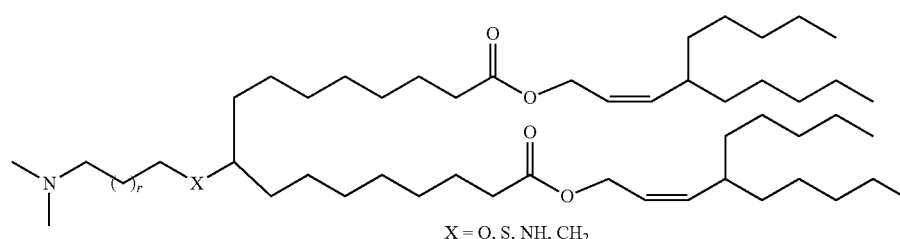
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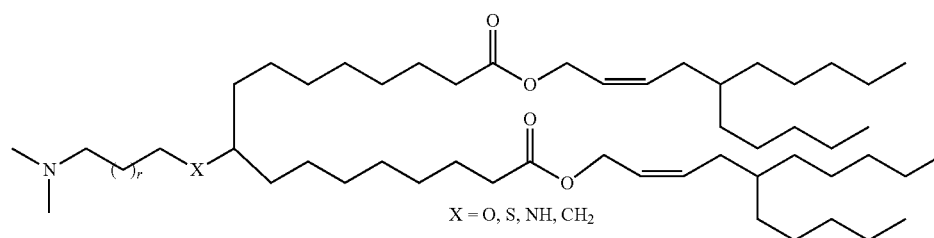
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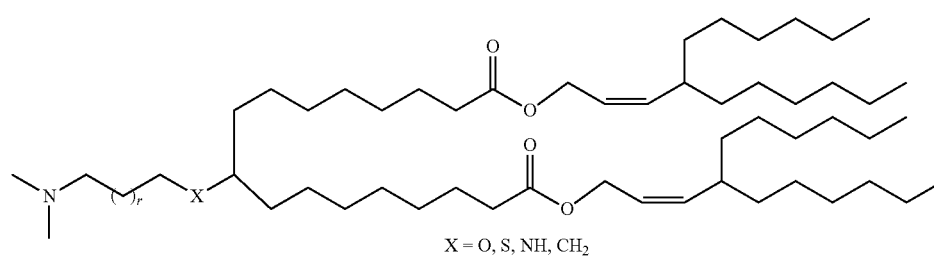
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r = 0, 1, or 2



r = 0, 1, or 2



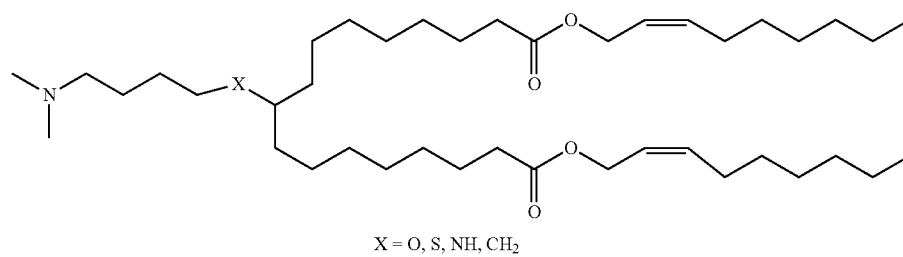
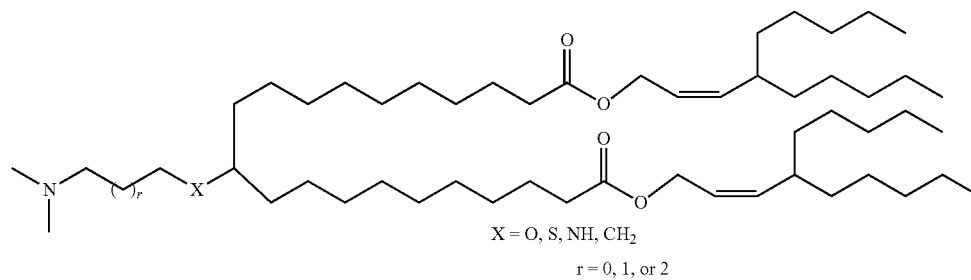
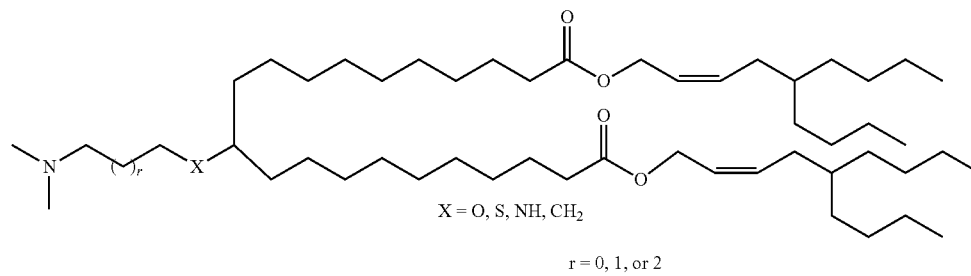
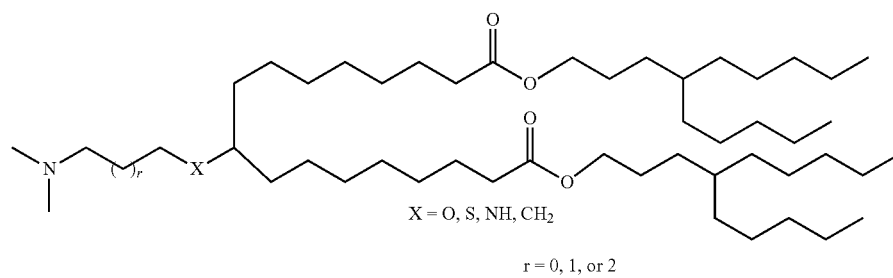
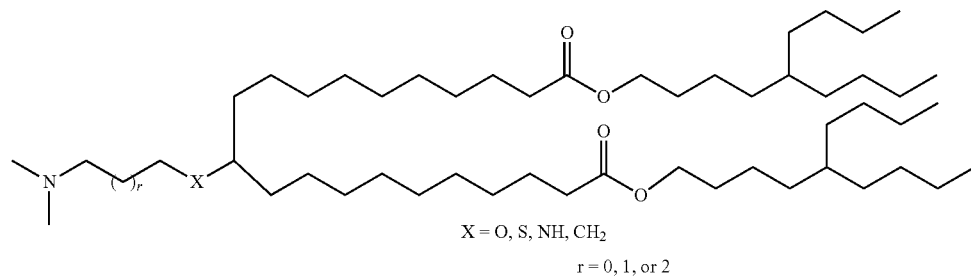
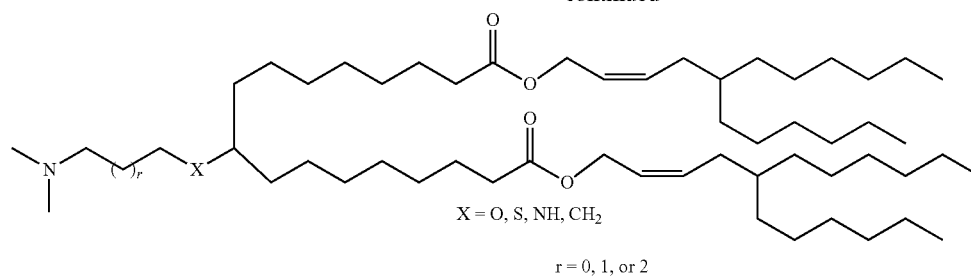
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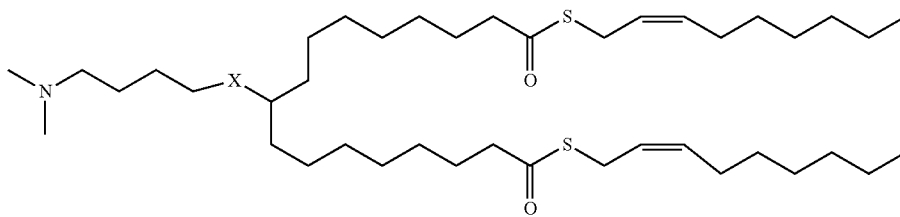
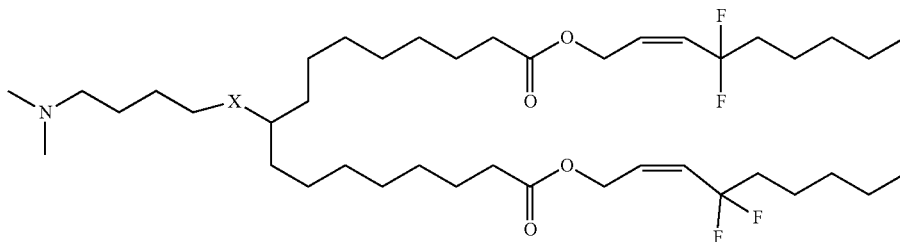
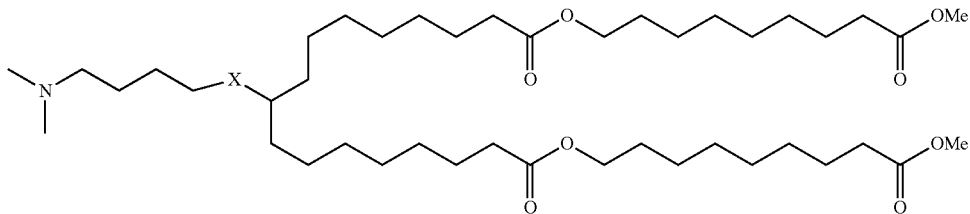
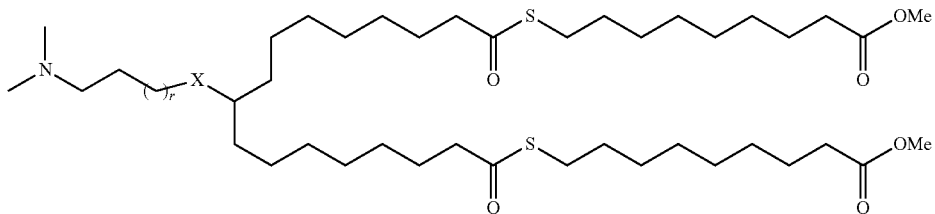
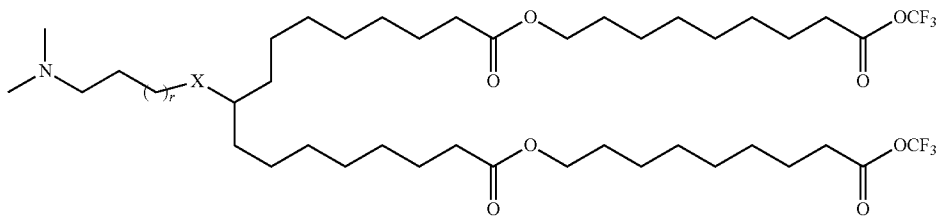
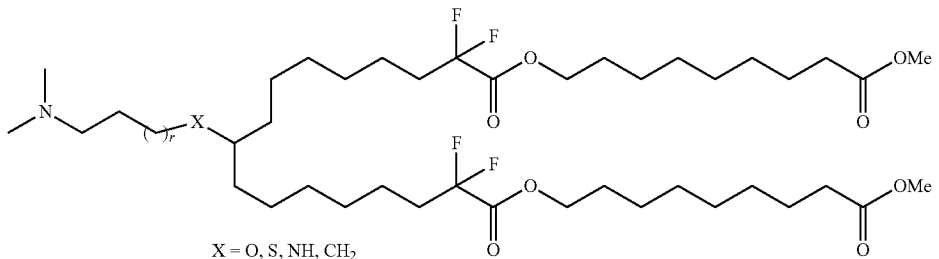


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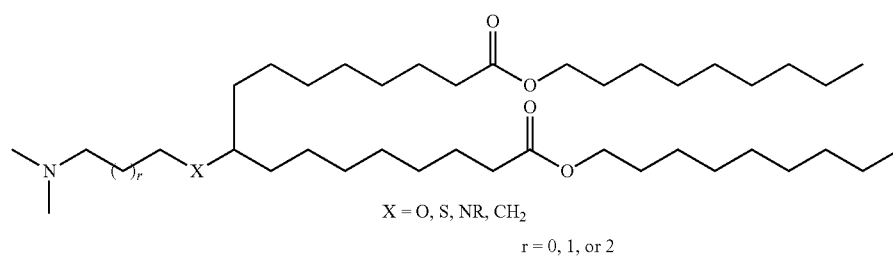
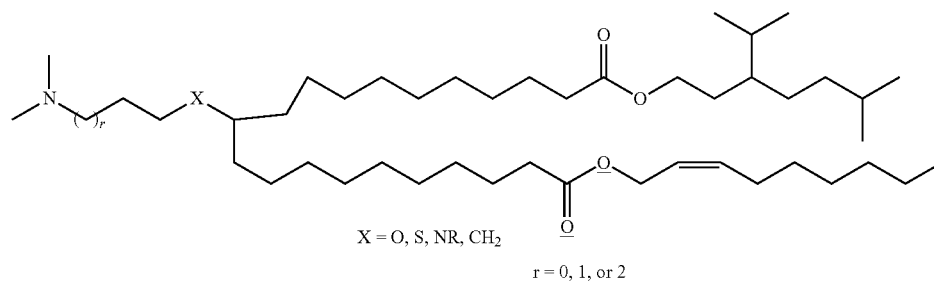
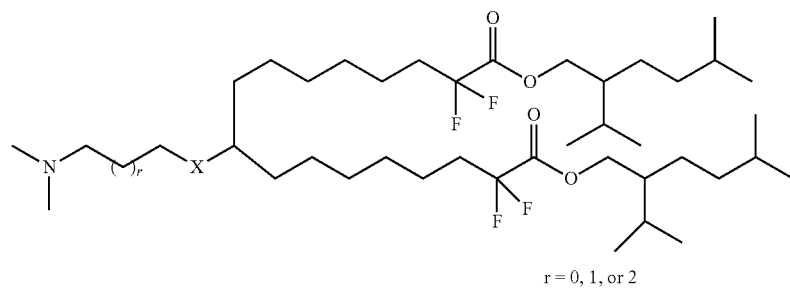
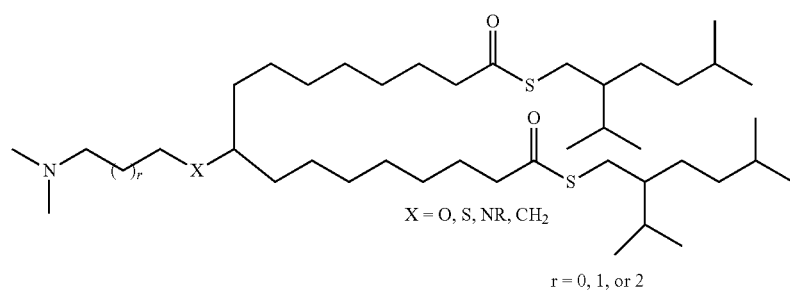
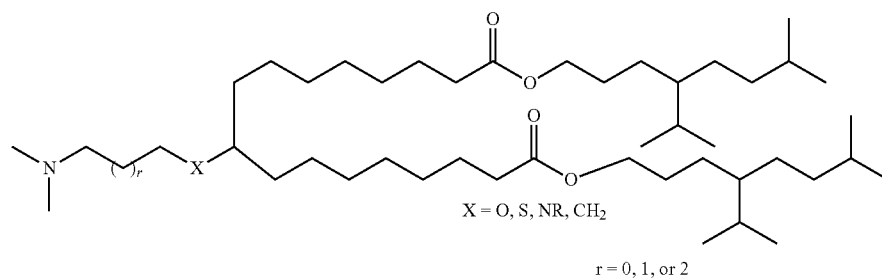
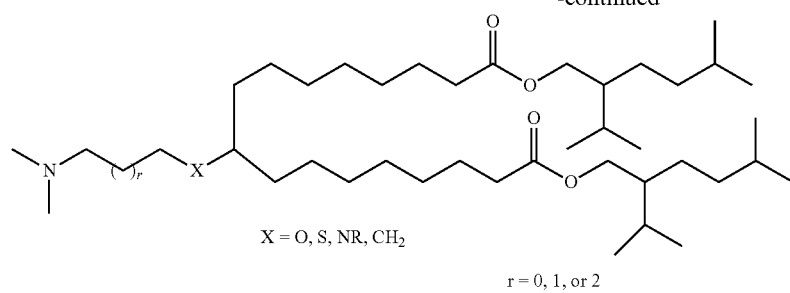

$$X = \text{O}, \text{S}, \text{NH}, \text{CH}_2$$

$$X = \text{O, S, NH, CH}_2$$

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$$X = \text{O, S, NH, CH}_2$$
$$r = 0, 1, \text{ or } 2$$

$$X = O, S, NR, CH_2$$
 $r = 0, 1, \text{ or } 2$ 
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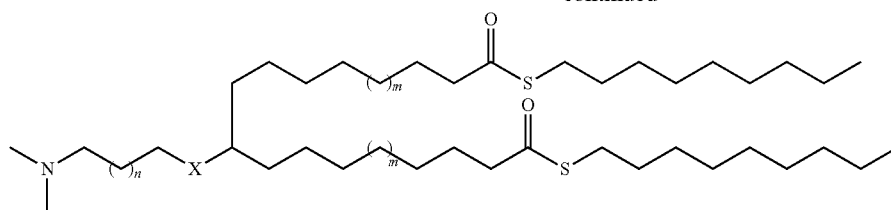


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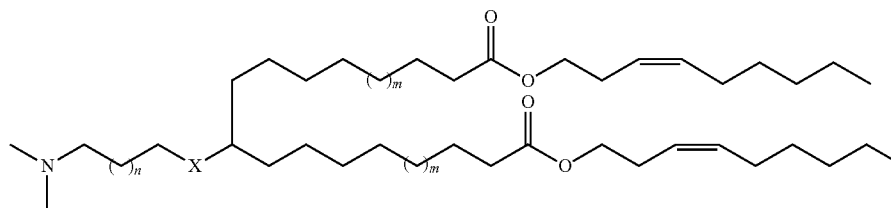
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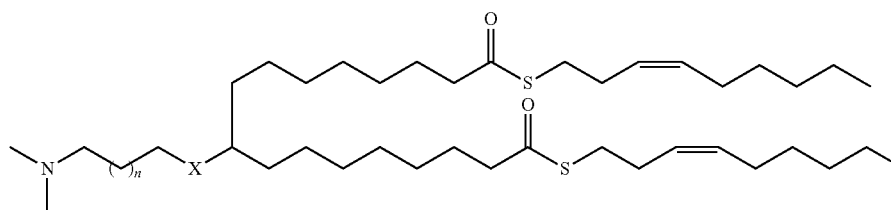
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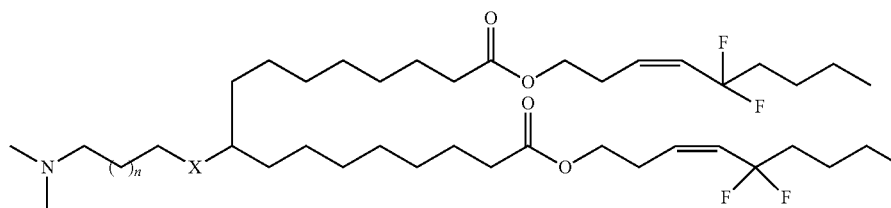
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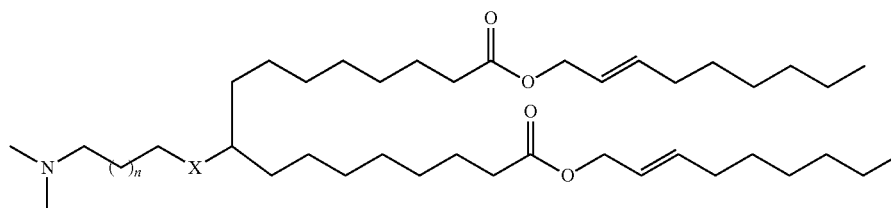
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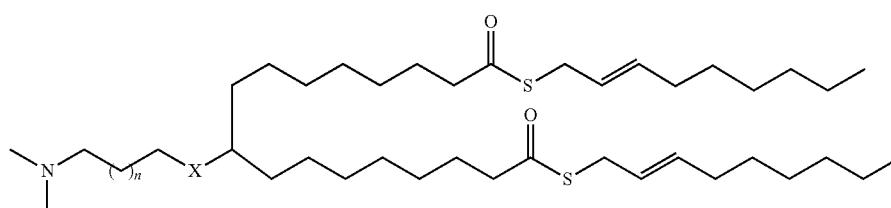
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n = 0, 1, or 2



n = 0, 1, or 2



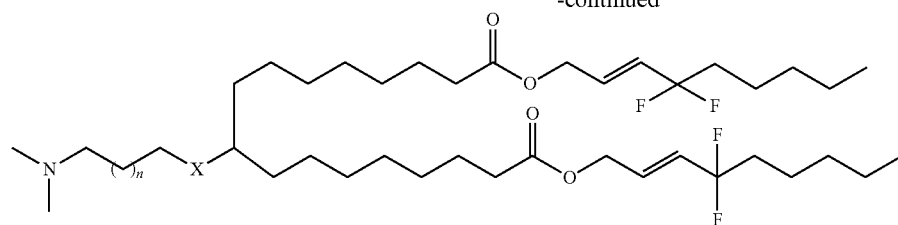
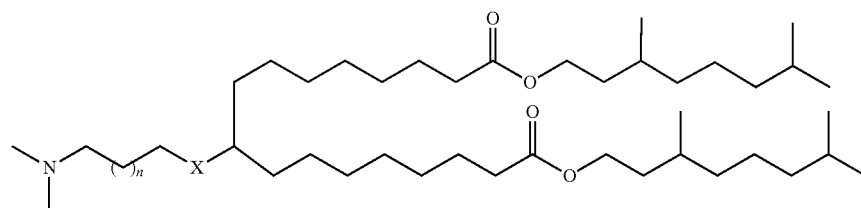
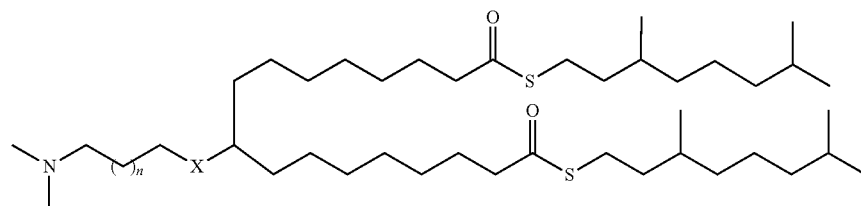
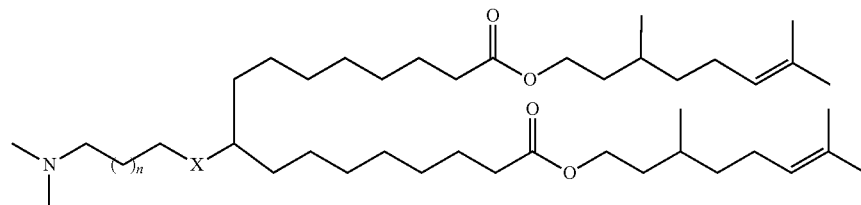
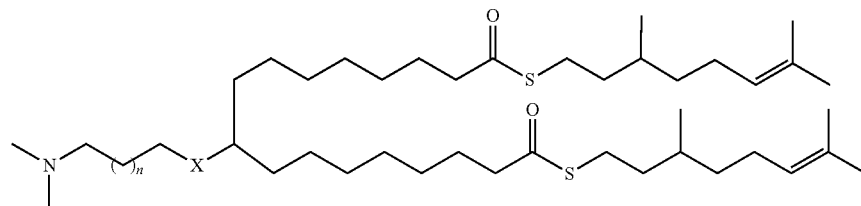
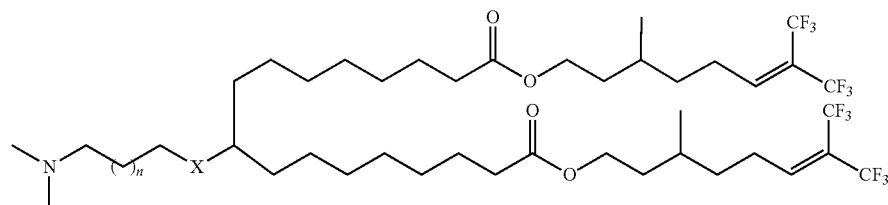
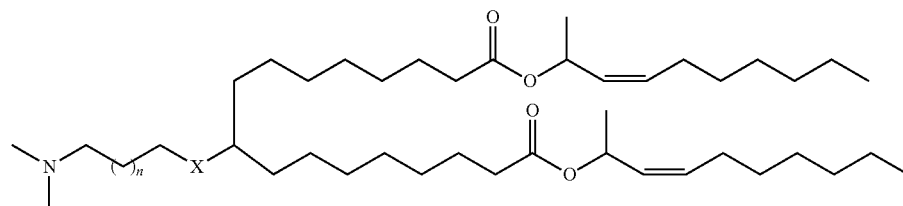
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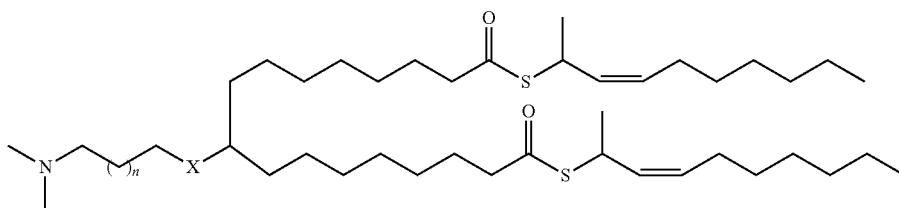
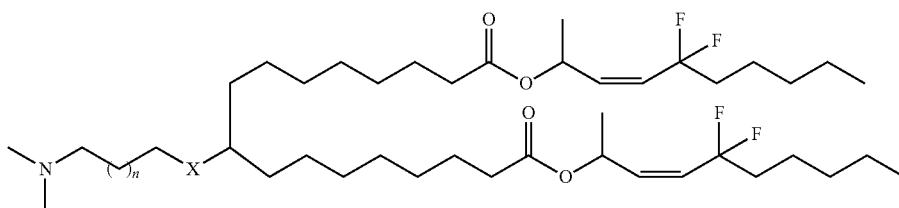
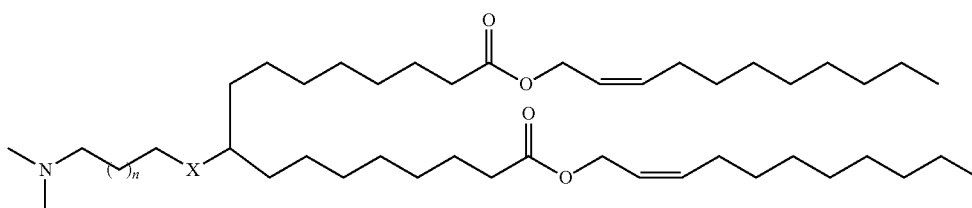
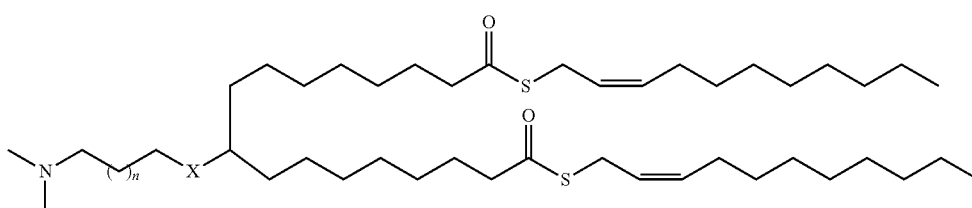
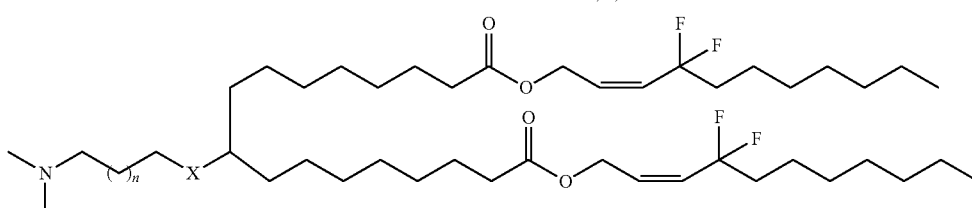
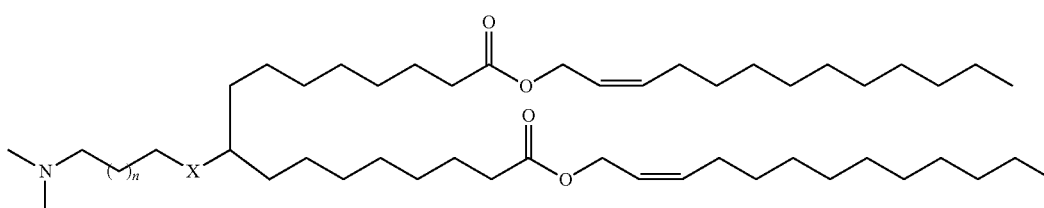
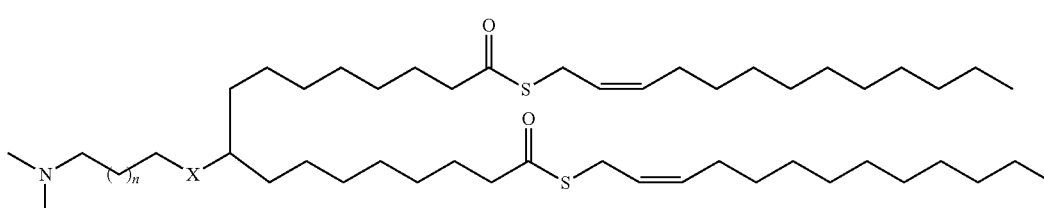
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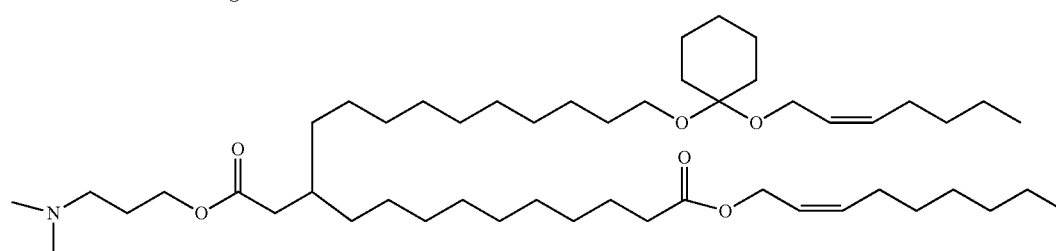
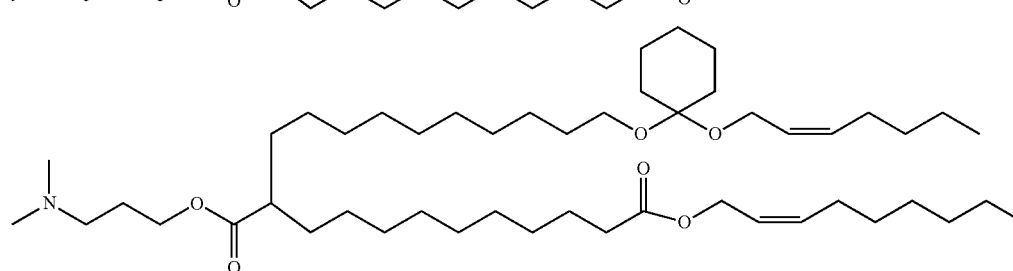
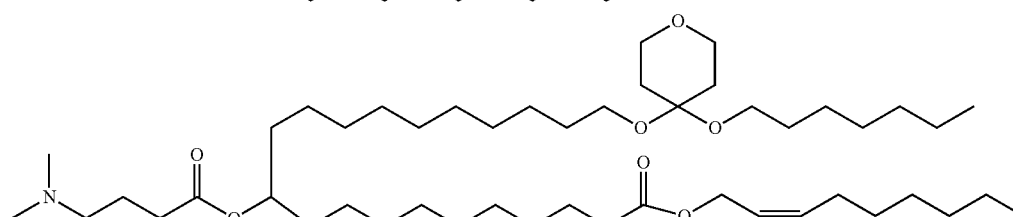
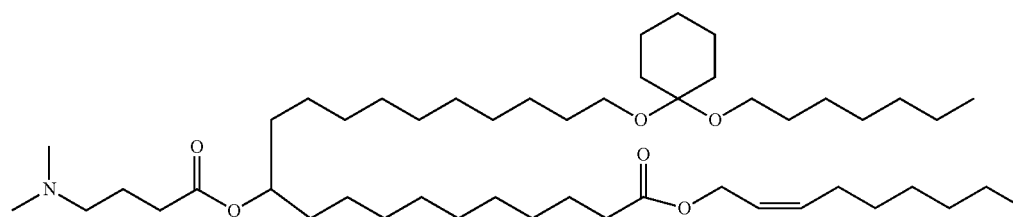
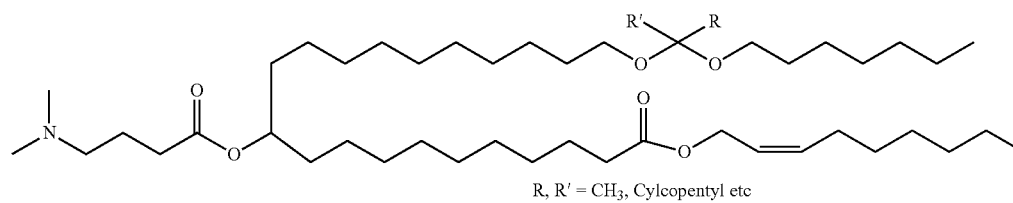
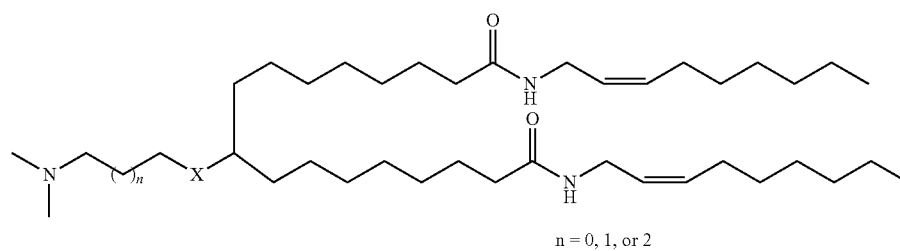
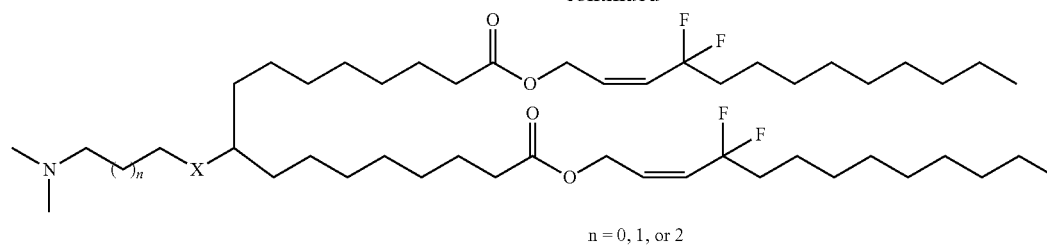

$$n = 0, 1, \text{ or } 2$$

$$n = 0, 1, \text{ or } 2$$
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$$n = 0, 1, \text{ or } 2$$

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$$n = 0, 1, \text{ or } 2$$

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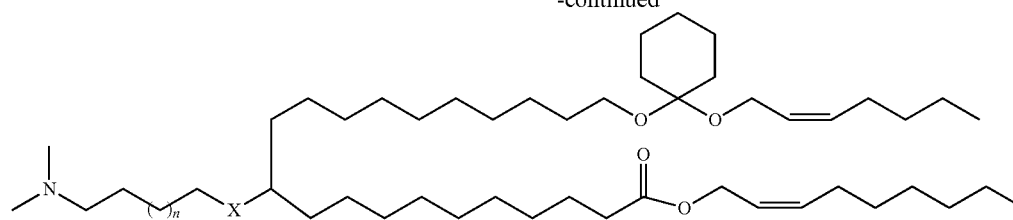
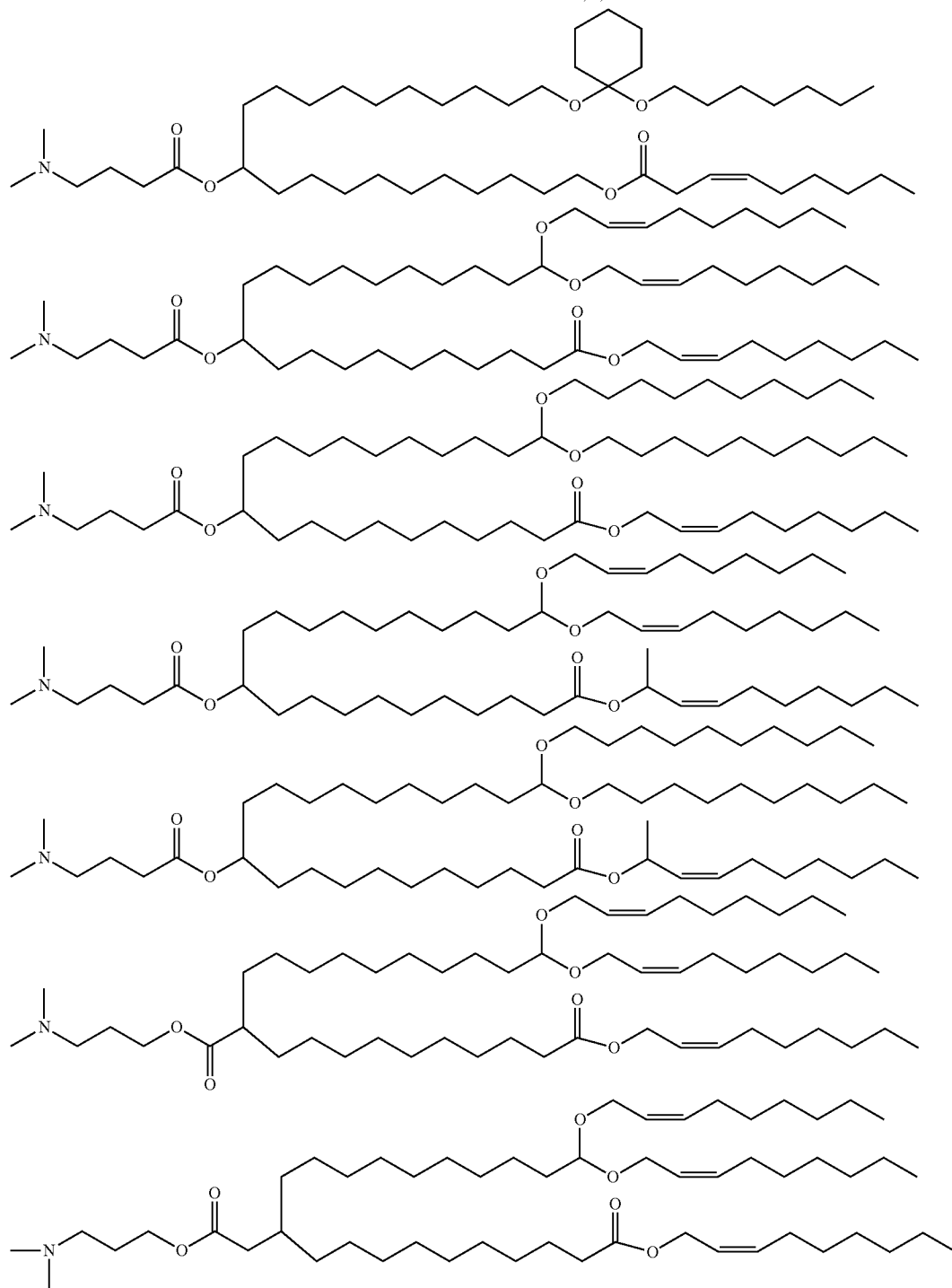


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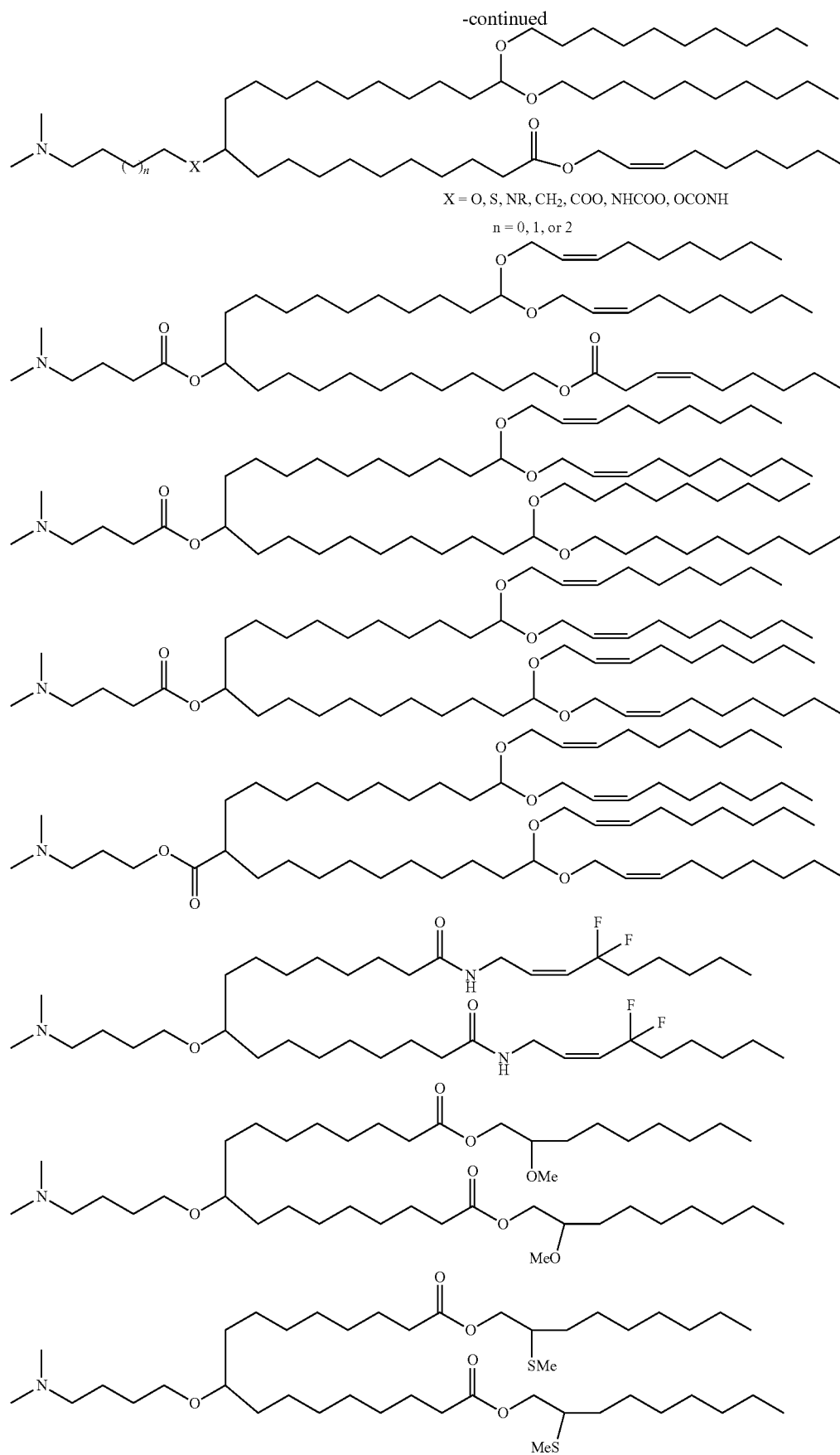
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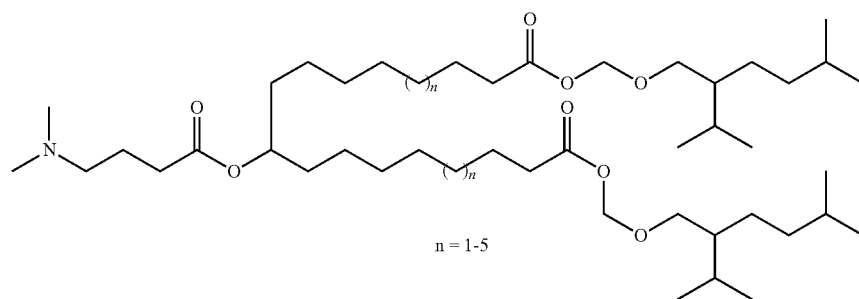
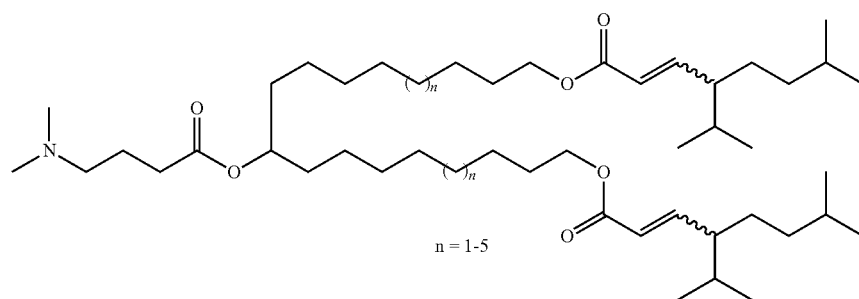
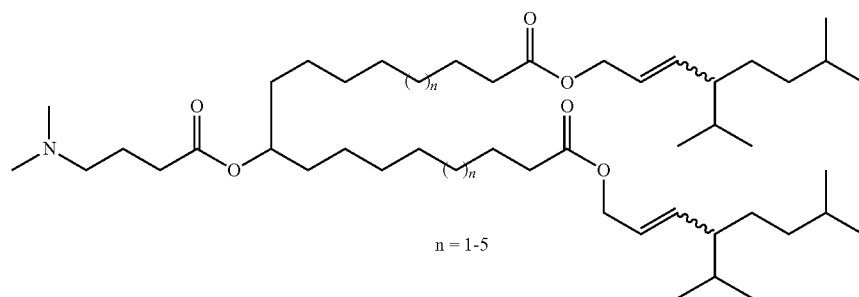
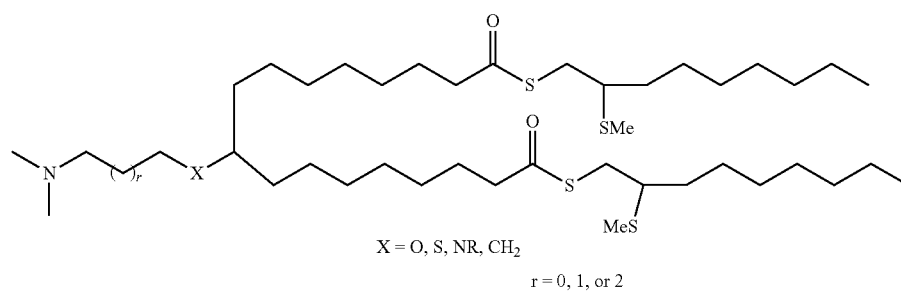
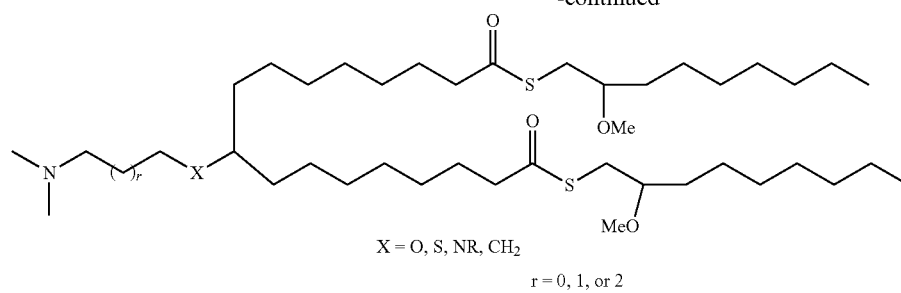


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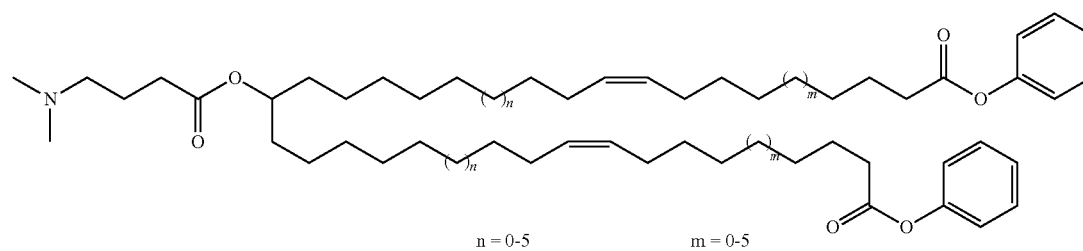
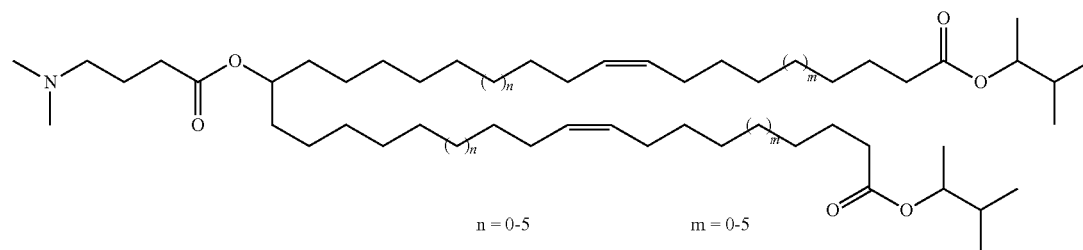
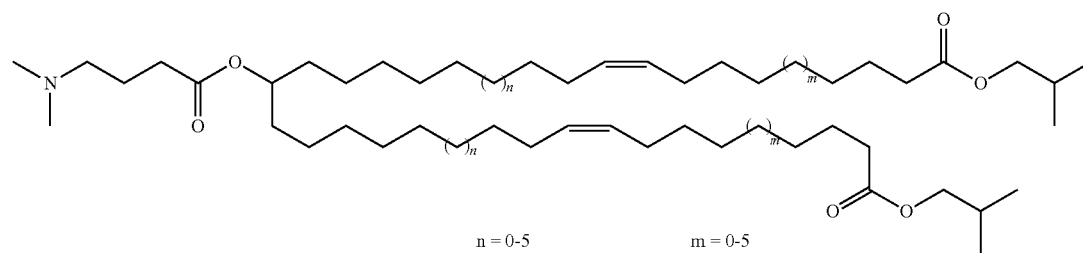
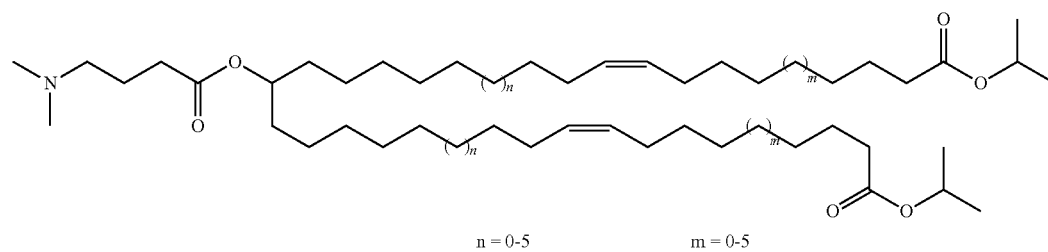
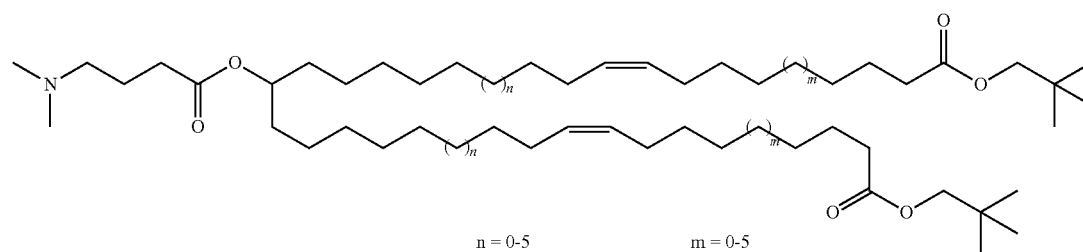
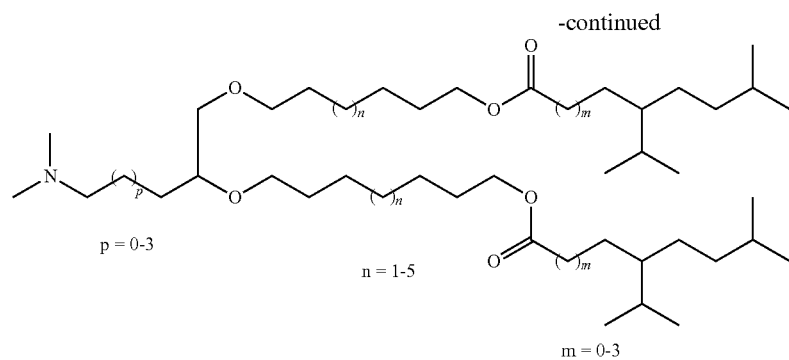
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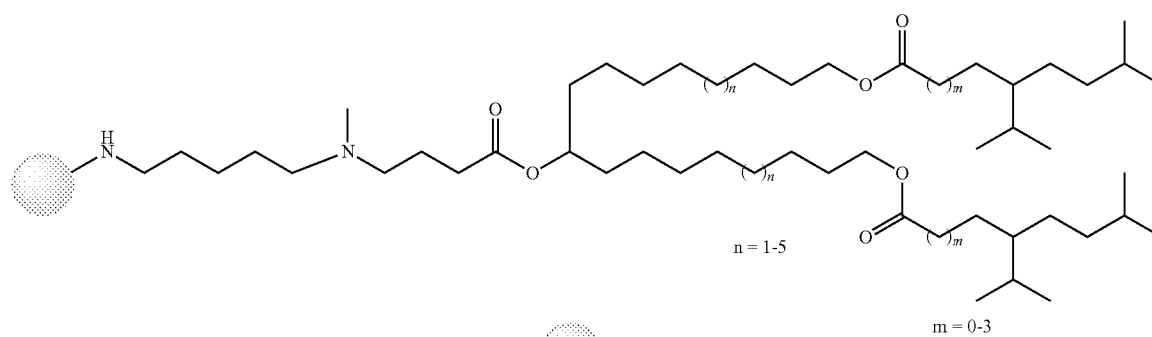
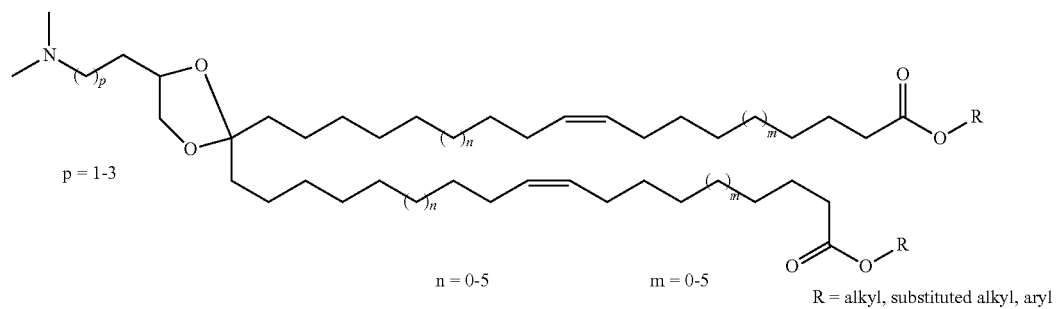
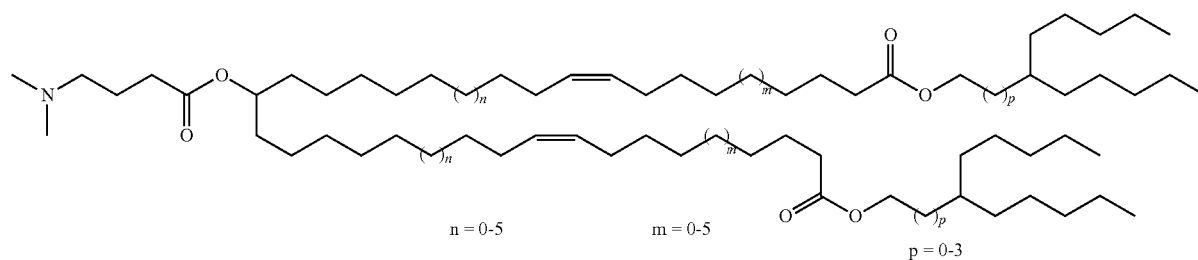
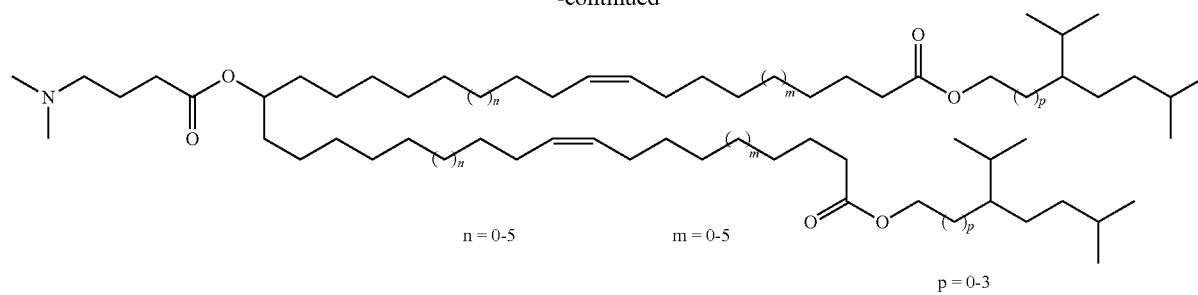


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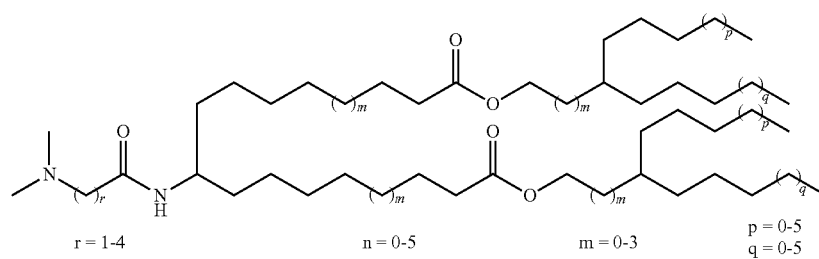
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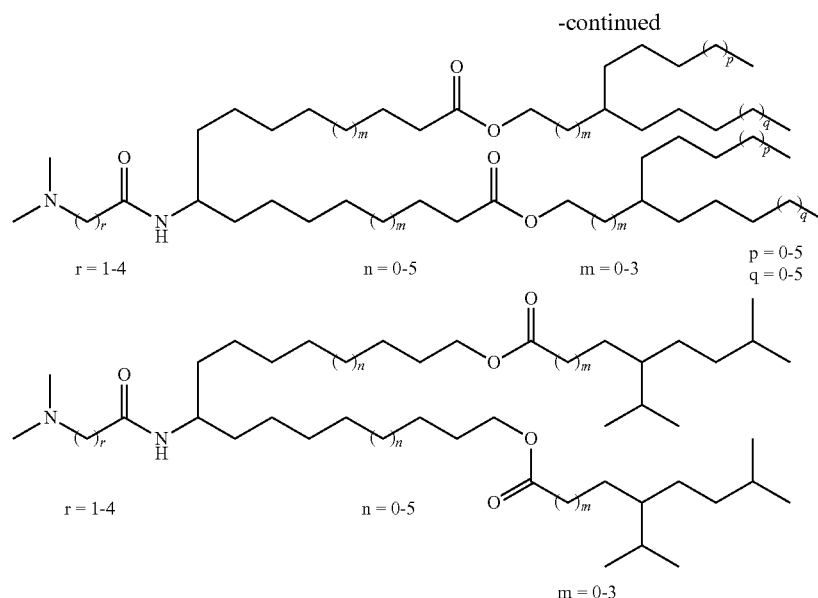
= Bodipy, Alexa-647 or other label (e.g., other fluorescent label)



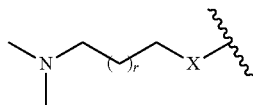
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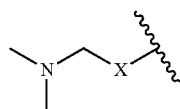
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Alternatively, for the compounds above having a head of the formula



(where X can be, for example, $-C(O)O-$), the head can have one methylene unit between the X group (or other functional group) and nitrogen atom. For example, the head can be:



Cationic lipids include those having alternative fatty acid groups and other dialkylamino groups than those shown, including those in which the alkyl substituents are different (e.g., N-ethyl-N-methylamino-, and N-propyl-N-ethylamino-).

In certain embodiments, the cationic lipids have at least one protonatable or deprotonatable group, such that the lipid is positively charged at a pH at or below physiological pH (e.g. pH 7.4), and neutral at a second pH, preferably at or above physiological pH. Such lipids are also referred to as cationic lipids. It will, of course, be understood that the addition or removal of protons as a function of pH is an equilibrium process, and that the reference to a charged or a neutral lipid refers to the nature of the predominant species and does not require that all of the lipid be present in the charged or neutral form. The lipids can have more than one protonatable or deprotonatable group, or can be zwitterionic.

In certain embodiments, protonatable lipids (i.e., cationic lipids) have a pK_a of the protonatable group in the range of about 4 to about 11. For example, the lipids can have a pK_a

of about 4 to about 7, e.g., from about 5 to about 7, such as from about 5.5 to about 6.8, when incorporated into lipid particles. Such lipids may be cationic at a lower pH formulation stage, while particles will be largely (though not completely) surface neutralized at physiological pH around pH 7.4.

In particular embodiments, the lipids are charged lipids. As used herein, the term "charged lipid" includes, but is not limited to, those lipids having one or two fatty acyl or fatty alkyl chains and a quaternary amino head group. The quaternary amine carries a permanent positive charge. The head group can optionally include an ionizable group, such as a primary, secondary, or tertiary amine that may be protonated at physiological pH. The presence of the quaternary amine can alter the pK_a of the ionizable group relative to the pK_a of the group in a structurally similar compound that lacks the quaternary amine (e.g., the quaternary amine is replaced by a tertiary amine).

Included in the instant invention is the free form of the cationic lipids described herein, as well as pharmaceutically acceptable salts and stereoisomers thereof. The cationic lipid can be a protonated salt of the amine cationic lipid. The term "free form" refers to the amine cationic lipids in non-salt form. The free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate.

The pharmaceutically acceptable salts of the instant cationic lipids can be synthesized from the cationic lipids of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic cationic lipids are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the cationic lipids of this invention include non-toxic salts of the cationic lipids of this invention as formed by reacting a basic instant

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cationic lipids with an inorganic or organic acid. For example, non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and trifluoroacetic (TFA).

When the cationic lipids of the present invention are acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, and zinc. In one embodiment, the base is selected from ammonium, calcium, magnesium, potassium and sodium. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N'-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, and tromethamine.

It will also be noted that the cationic lipids of the present invention may potentially be internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

One or more additional cationic lipids, which carry a net positive charge at about physiological pH, in addition to those specifically described above, may also be included in the lipid particles and compositions described herein. Such cationic lipids include, but are not limited to N,N-dioleoyl-N,N-dimethylammonium chloride ("DODAC"); N-(2,3-dioleoyloxy)propyl-N,N,N-triethylammonium chloride ("DOTMA"); N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); N-(2,3-dioleoyloxy)propyl-N,N,N-trimethylammonium chloride ("DOTAP"); 1,2-Dioleoyloxy-3-trimethylaminopropane chloride salt ("DOTAP.Cl"); 3 β -(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol"); N-(1-(2,3-dioleoyloxy)propyl)-N-2-(spermincarboxamido)ethyl-N,N-dimethylammonium trifluoroacetate ("DOSPA"); dioctadecylamidoglycyl carboxyspermine

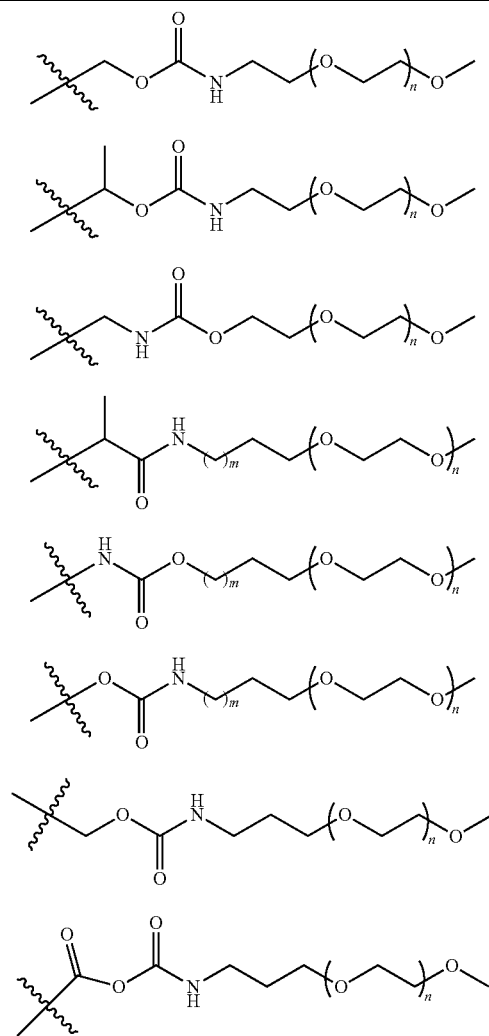
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("DOGS"), 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE"), 1,2-dioleoyl-3-dimethylammonium propane ("DODAP"), N, N-dimethyl-2,3-dioleoyloxypropylamine ("DODMA"), and N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE"). Additionally, a number of commercial preparations of cationic lipids can be used, such as, e.g., LIPOFECTIN (including DOTMA and DOPE, available from GIBCO/BRL), and LIPOFECTAMINE (comprising DOSPA and DOPE, available from GIBCO/BRL).

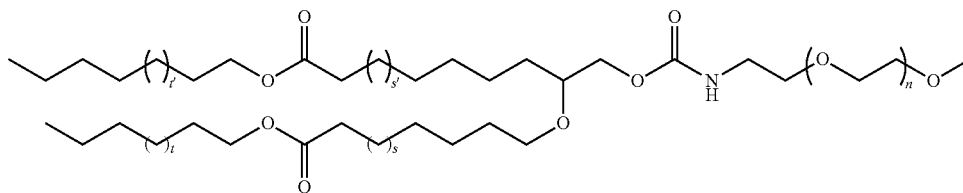
PEG Lipids

Suitable head groups for the PEG lipids include, but are not limited to those shown in Table 3 below.

TABLE 3



Representative PEG lipids include, but are not limited to:

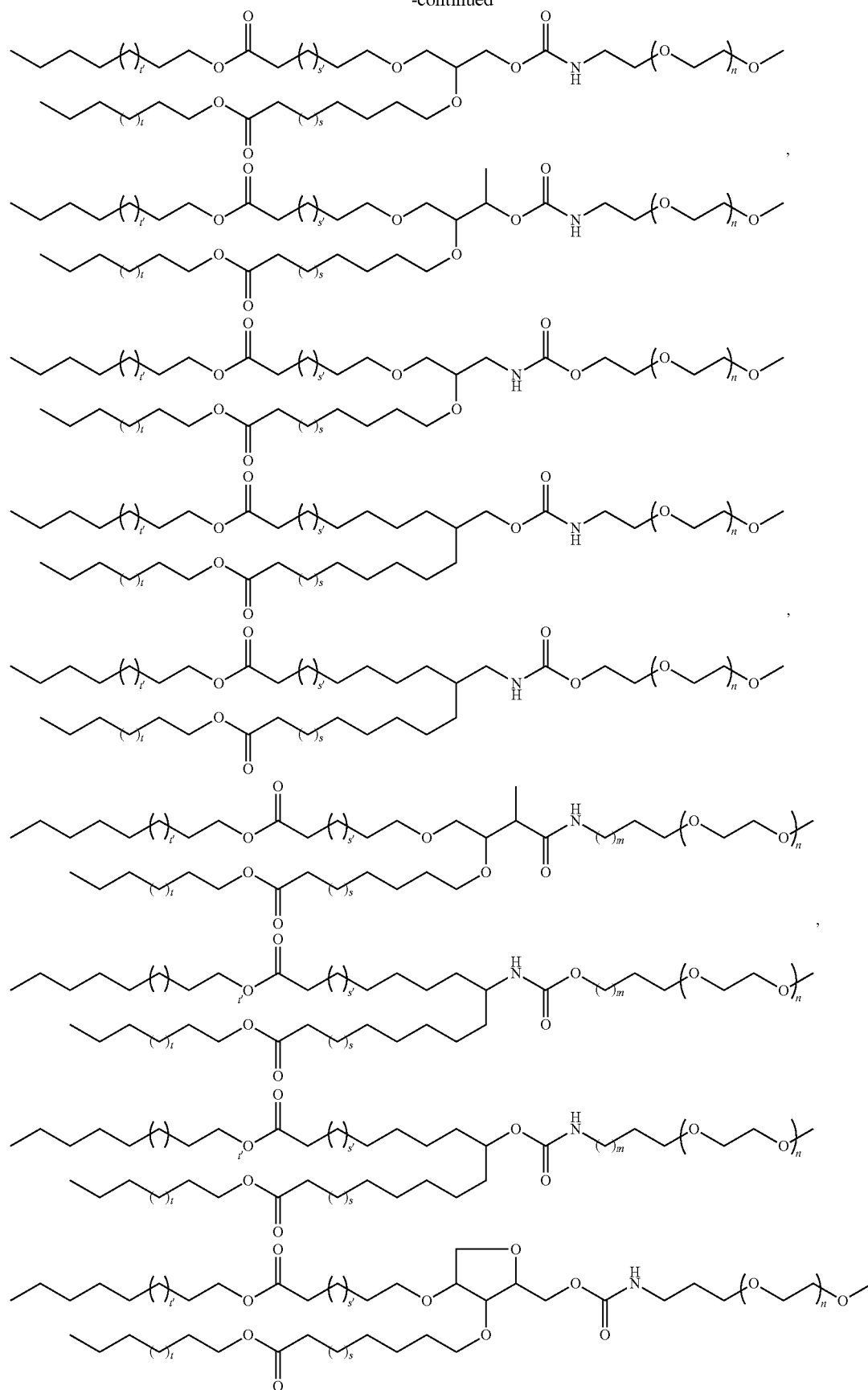


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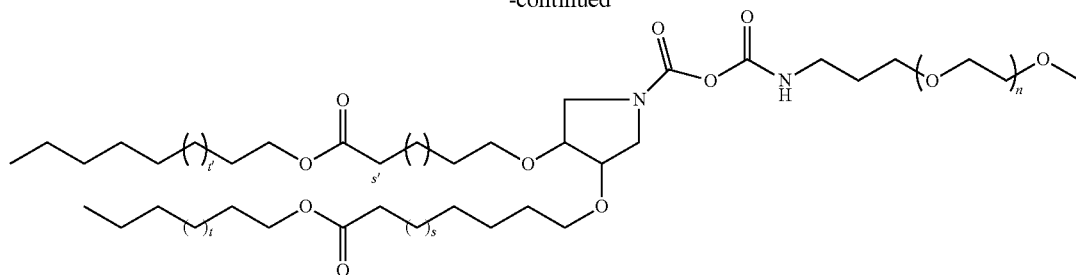


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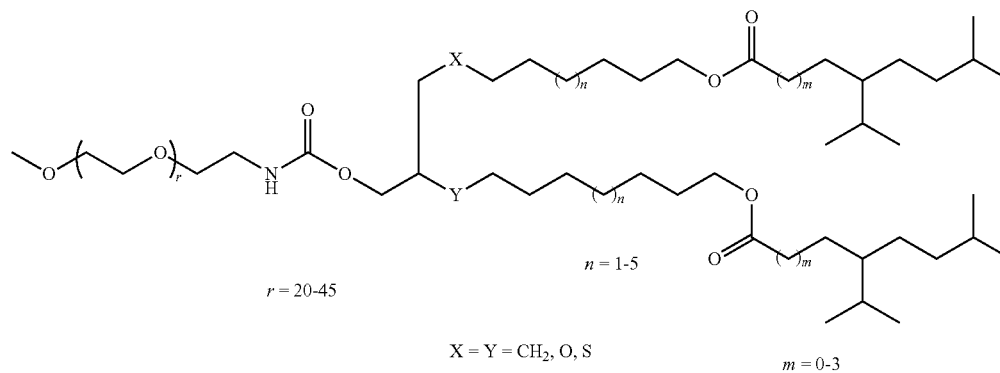
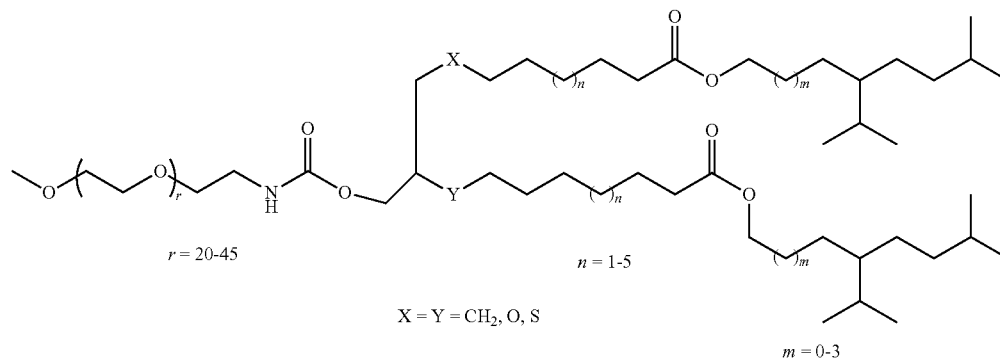
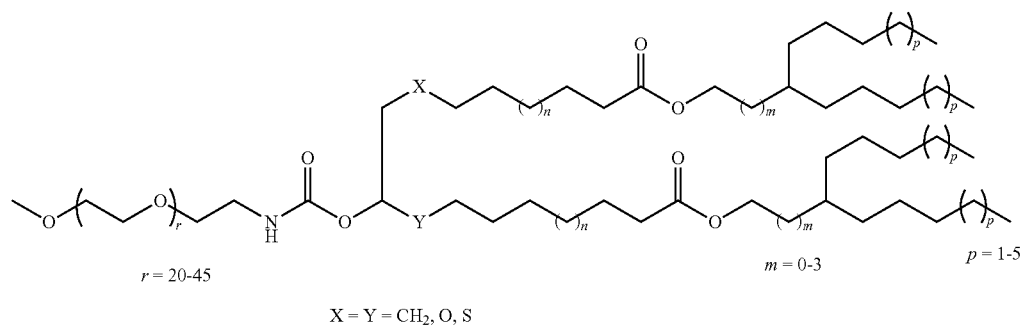
wherein

n is an integer from 10 to 100 (e.g. 20-50 or 40-50);

s, s', t and t' are independently 0, 1, 2, 3, 4, 5, 6 or 7; and

m is 1, 2, 3, 4, 5, or 6.

Other representative PEG lipids include, but are not limited to:

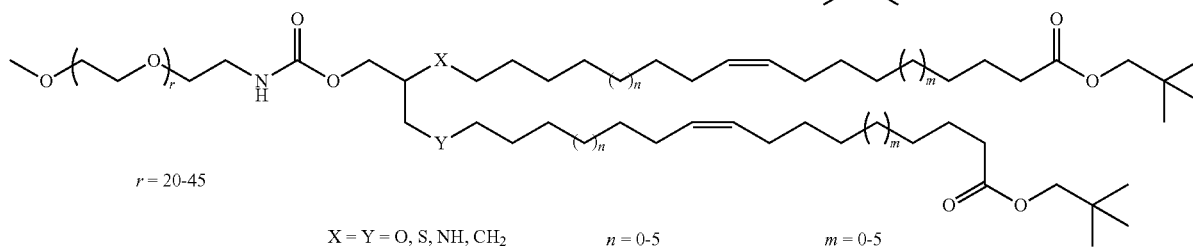
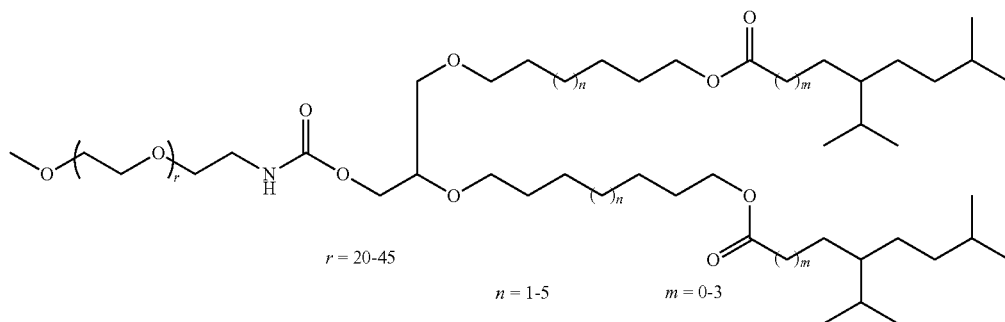
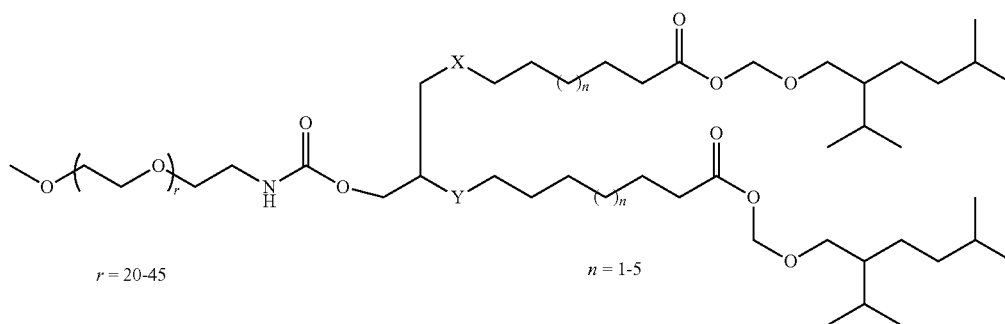
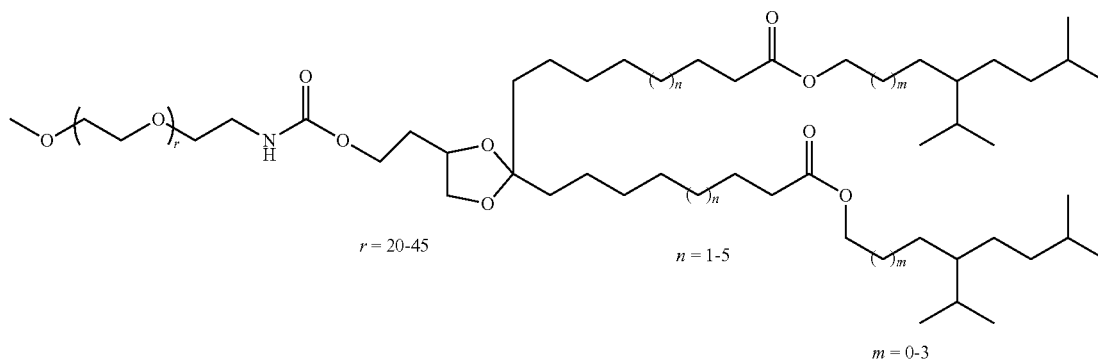
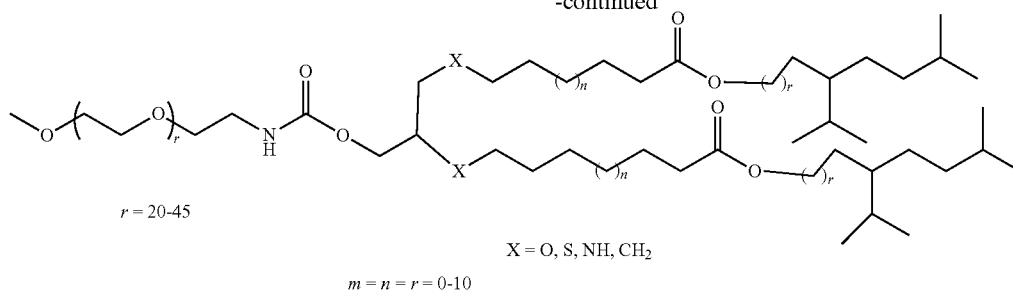


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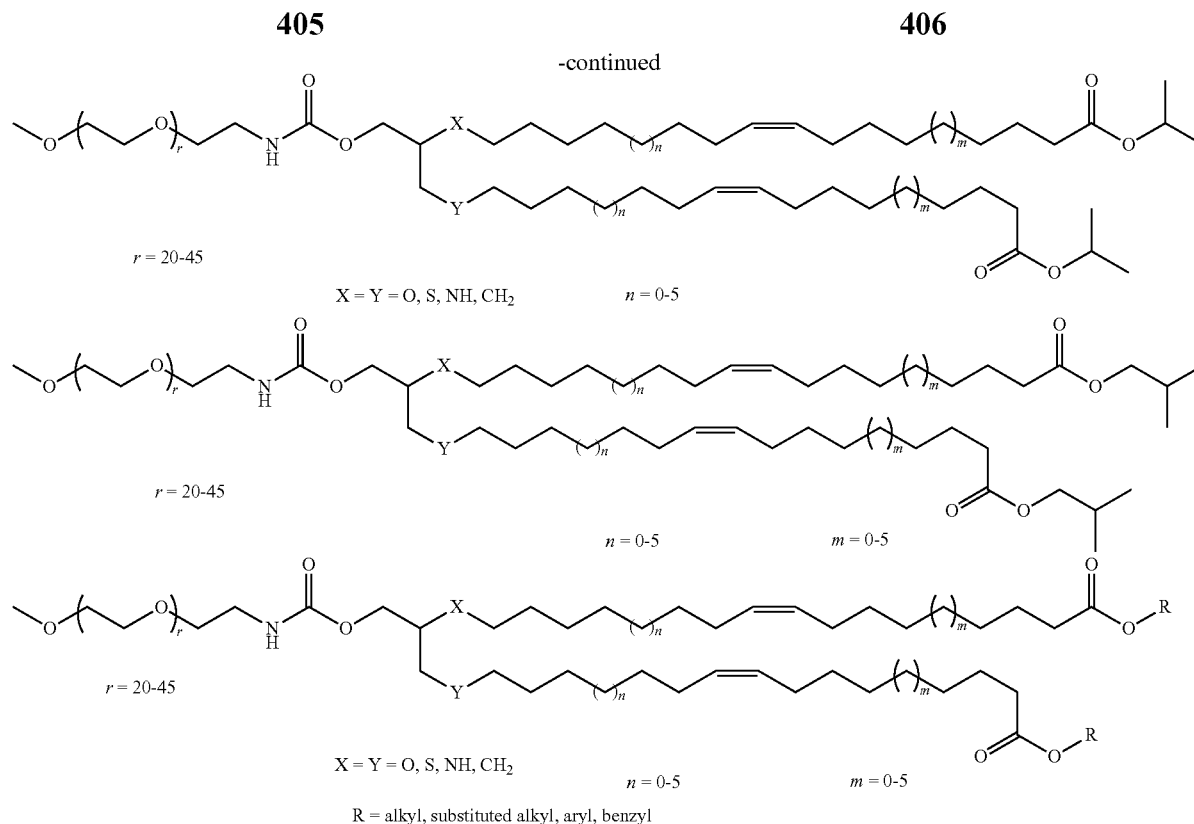
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The Other Lipid Components

The lipid particles and compositions described herein may also include one or more neutral lipids. Neutral lipids, when present, can be any of a number of lipid species which exist either in an uncharged or neutral zwitterionic form at physiological pH. Such lipids include, for example, diacylphosphatidylcholine, diacylphosphatidylethanolamine, ceramide, sphingomyelin, dihydrosphingomyelin, cephalin, and cerebroside. In one embodiment, the neutral lipid component is a lipid having two acyl groups (e.g., diacylphosphatidylcholine and diacylphosphatidylethanolamine). In one embodiment, the neutral lipid contains saturated fatty acids with carbon chain lengths in the range of C₁₀ to C₂₀. In another embodiment, the neutral lipid includes mono or diunsaturated fatty acids with carbon chain lengths in the range of C₁₀ to C₂₀. Suitable neutral lipids include, but are not limited to, DSPC, DPPC, POPC, DOPE, DSPE, and SM.

The lipid particles and compositions described herein may also include one or more lipids capable of reducing aggregation. Examples of lipids that reduce aggregation of particles during formation include polyethylene glycol (PEG)-modified lipids (PEG lipids, such as PEG-DMG and PEG-DMA), monosialoganglioside Gm1, and polyamide oligomers ("PAO") such as (described in U.S. Pat. No. 6,320,017, which is incorporated by reference in its entirety). Suitable PEG lipids include, but are not limited to, PEG-modified phosphatidylethanolamine and phosphatidic acid, PEG-ceramide conjugates (e.g., PEG-CerC14 or PEG-CerC20) (such as those described in U.S. Pat. No. 5,820,873, incorporated herein by reference), PEG-modified dialkylamines and PEG-modified 1,2-diacyloxypropan-3-amines, PEG-modified diacylglycerols and dialkylglycerols, mPEG (mw2000)-diastearoylphosphatidylethanolamine (PEG-DSPE).

The lipid particles and compositions may include a sterol, such as cholesterol.

Lipid Particles

In a further aspect, the present invention relates to lipid particles that include one or more of the cationic lipids described herein. In one embodiment, the lipid particle includes one or more compounds of formula I-VII.

Lipid particles include, but are not limited to, liposomes. As used herein, a liposome is a structure having lipid-containing membranes enclosing an aqueous interior.

Another embodiment is a nucleic acid-lipid particle (e.g., a SNALP) comprising a cationic lipid of the present invention, a non-cationic lipid (such as a neutral lipid), optionally a PEG-lipid conjugate (such as the lipids for reducing aggregation of lipid particles discussed herein), optionally a sterol (e.g., cholesterol), and a nucleic acid. As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle. A SNALP represents a particle made from lipids, wherein the nucleic acid (e.g., an interfering RNA) is encapsulated within the lipids. In certain instances, SNALPs are useful for systemic applications, as they can exhibit extended circulation lifetimes following intravenous (i.v.) injection, they can accumulate at distal sites (e.g., sites physically separated from the administration site), and they can mediate silencing of target gene expression at these distal sites. The nucleic acid may be complexed with a condensing agent and encapsulated within a SNALP as set forth in International Publication No. WO 00/03683, the disclosure of which is herein incorporated by reference in its entirety.

For example, the lipid particle may include a cationic lipid, a fusion-promoting lipid (e.g., DPPC), a neutral lipid, cholesterol, and a PEG-modified lipid. In one embodiment, the lipid particle includes the above lipid mixture in molar ratios of about 20-70% cationic lipid: 0.1-50% fusion pro-

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moting lipid: 5-45% neutral lipid: 20-55% cholesterol: 0.5-15% PEG-modified lipid (based upon 100% total moles of lipid in the lipid particle).

In another embodiment of the lipid particle, the cationic lipid is present in a mole percentage of about 20% and about 60%; the neutral lipid is present in a mole percentage of about 5% to about 25%; the sterol is present in a mole percentage of about 25% to about 55%; and the PEG lipid is PEG-DMA, PEG-DMG, or a combination thereof, and is present in a mole percentage of about 0.5% to about 15% (based upon 100% total moles of lipid in the lipid particle).

In particular embodiments, the molar lipid ratio, with regard to mol % cationic lipid/DSPC/Chol/PEG-DMG or PEG-DMA is approximately 40/10/40/10, 35/15/40/10 or 52/13/30/5. This mixture may be further combined with a fusion-promoting lipid in a molar ratio of 0.1-50%, 0.1-50%, 0.5-50%, 1-50%, 5%-45%, 10%-40%, or 15%-35%. In other words, when a 40/10/40/10 mixture of lipid/DSPC/Chol/PEG-DMG or PEG-DMA is combined with a fusion-promoting peptide in a molar ratio of 50%, the resulting lipid particles can have a total molar ratio of (mol % cationic lipid/DSPC/Chol/PEG-DMG or PEG-DMA/fusion-promoting peptide) 20/5/20/5/50. In another embodiment, the neutral lipid, DSPC, in these compositions is replaced with POPC, DPPC, DOPE or SM.

In one embodiment, the lipid particles comprise a cationic lipid of the present invention, a neutral lipid, a sterol and a PEG-modified lipid. In one embodiment, the lipid particles include from about 25% to about 75% on a molar basis of cationic lipid, e.g., from about 35 to about 65%, from about 45 to about 65%, about 60%, about 57.5%, about 57.1%, about 50% or about 40% on a molar basis. In one embodiment, the lipid particles include from about 0% to about 15% on a molar basis of the neutral lipid, e.g., from about 3 to about 12%, from about 5 to about 10%, about 15%, about 10%, about 7.5%, about 7.1% or about 0% on a molar basis. In one embodiment, the neutral lipid is DPPC. In one embodiment, the neutral lipid is DSPC. In one embodiment, the formulation includes from about 5% to about 50% on a molar basis of the sterol, e.g., about 15 to about 45%, about 20 to about 40%, about 48%, about 40%, about 38.5%, about 35%, about 34.4%, about 31.5% or about 31% on a molar basis. In one embodiment, the sterol is cholesterol.

The lipid particles described herein may further include one or more therapeutic agents. In a preferred embodiment, the lipid particles include a nucleic acid (e.g., an oligonucleotide), such as siRNA or miRNA.

In one embodiment, the lipid particles include from about 0.1% to about 20% on a molar basis of the PEG-modified lipid, e.g., about 0.5 to about 10%, about 0.5 to about 5%, about 10%, about 5%, about 3.5%, about 1.5%, about 0.5%, or about 0.3% on a molar basis. In one embodiment, the PEG-modified lipid is PEG-DMG. In one embodiment, the PEG-modified lipid is PEG-c-DMA. In one embodiment, the lipid particles include 25-75% of cationic lipid, 0.5-15% of the neutral lipid, 5-50% of the sterol, and 0.5-20% of the PEG-modified lipid on a molar basis.

In one embodiment, the lipid particles include 35-65% of cationic lipid, 3-12% of the neutral lipid, 15-45% of the sterol, and 0.5-10% of the PEG-modified lipid on a molar basis. In one embodiment, the lipid particles include 45-65% of cationic lipid, 5-10% of the neutral lipid, 25-40% of the sterol, and 0.5-5% of the PEG-modified lipid on a molar basis. In one embodiment, the PEG modified lipid comprises a PEG molecule of an average molecular weight of 2,000 Da. In one embodiment, the PEG modified lipid is PEG-distyryl glycerol (PEG-DSG).

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In one embodiment, the ratio of lipid:siRNA is at least about 0.5:1, at least about 1:1, at least about 2:1, at least about 3:1, at least about 4:1, at least about 5:1, at least about 6:1, at least about 7:1, at least about 11:1 or at least about 33:1. In one embodiment, the ratio of lipid:siRNA ratio is between about 1:1 to about 35:1, about 3:1 to about 15:1, about 4:1 to about 15:1, or about 5:1 to about 13:1. In one embodiment, the ratio of lipid:siRNA ratio is between about 0.5:1 to about 12:1.

In one embodiment, the lipid particles are nanoparticles. In additional embodiments, the lipid particles have a mean diameter size of from about 50 nm to about 300 nm, such as from about 50 nm to about 250 nm, for example, from about 50 nm to about 200 nm.

In one embodiment, a lipid particle containing a cationic lipid of any of the embodiments described herein has an in vivo half life ($t_{1/2}$) (e.g., in the liver, spleen or plasma) of less than about 3 hours, such as less than about 2.5 hours, less than about 2 hours, less than about 1.5 hours, less than about 1 hour, less than about 0.5 hour or less than about 0.25 hours.

In another embodiment, a lipid particle containing a cationic lipid of any of the embodiments described herein has an in vivo half life ($t_{1/2}$) (e.g., in the liver, spleen or plasma) of less than about 10% (e.g., less than about 7.5%, less than about 5%, less than about 2.5%) of that for the same cationic lipid without the biodegradable group or groups.

Additional Components

The lipid particles and compositions described herein can further include one or more antioxidants. The antioxidant stabilizes the lipid particle and prevents, decreases, and/or inhibits degradation of the cationic lipid and/or active agent present in the lipid particles. The antioxidant can be a hydrophilic antioxidant, a lipophilic antioxidant, a metal chelator, a primary antioxidant, a secondary antioxidant, salts thereof, and mixtures thereof. In certain embodiments, the antioxidant comprises a metal chelator such as EDTA or salts thereof, alone or in combination with one, two, three, four, five, six, seven, eight, or more additional antioxidants such as primary antioxidants, secondary antioxidants, or other metal chelators. In one preferred embodiment, the antioxidant comprises a metal chelator such as EDTA or salts thereof in a mixture with one or more primary antioxidants and/or secondary antioxidants. For example, the antioxidant may comprise a mixture of EDTA or a salt thereof, a primary antioxidant such as α -tocopherol or a salt thereof, and a secondary antioxidant such as ascorbyl palmitate or a salt thereof. In one embodiment, the antioxidant comprises at least about 100 mM citrate or a salt thereof. Examples of antioxidants include, but are not limited to, hydrophilic antioxidants, lipophilic antioxidants, and mixtures thereof. Non-limiting examples of hydrophilic antioxidants include chelating agents (e.g., metal chelators) such as ethylenediaminetetraacetic acid (EDTA), citrate, ethylene glycol tetraacetic acid (EGTA), 1,2-bis(o-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid (BAPTA), diethylene triamine pentaacetic acid (DTPA), 2,3-dimercapto-1-propane-sulfonic acid (DMPS), dimercaptosuccinic acid (DMSA), cc-lipoic acid, salicylaldehyde isonicotinoyl hydrazone (SIH), hexyl thioethylamine hydrochloride (HTA), desferri-oxamine, salts thereof, and mixtures thereof. Additional hydrophilic antioxidants include ascorbic acid, cysteine, glutathione, dihydrolipoic acid, 2-mercaptoethane sulfonic acid, 2-mercaptobenzimidazole sulfonic acid, 6-hydroxy-2, 5,7,8-tetramethylchroman-2-carboxylic acid, sodium metabisulfite, salts thereof, and mixtures thereof. Non-limiting examples of lipophilic antioxidants include vitamin E isomers such as α -, β -, γ -, and δ -tocopherols and α -, β -, γ -, and

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δ -tocotrienols; polyphenols such as 2-tert-butyl-4-methyl phenol, 2-tert-butyl-5-methyl phenol, and 2-tert-butyl-6-methyl phenol; butylated hydroxyanisole (BHA) (e.g., 2-tert-butyl-4-hydroxyanisole and 3-tert-butyl-4-hydroxyanisole); butylhydroxytoluene (BHT); tert-butylhydroquinone (TBHQ); ascorbyl palmitate; *rac*-propyl gallate; salts thereof; and mixtures thereof. Suitable antioxidants and formulations containing such antioxidants are described in International Publication No. WO 2011/066651, which is hereby incorporated by reference.

In another embodiment, the lipid particles or compositions contain the antioxidant EDTA (or a salt thereof), the antioxidant citrate (or a salt thereof), or EDTA (or a salt thereof) in combination with one or more (e.g., a mixture of) primary and/or secondary antioxidants such as α -tocopherol (or a salt thereof) and/or ascorbyl palmitate (or a salt thereof).

In one embodiment, the antioxidant is present in an amount sufficient to prevent, inhibit, or reduce the degradation of the cationic lipid present in the lipid particle. For example, the antioxidant may be present at a concentration of at least about or about 0.1 mM, 0.5 mM, 1 mM, 10 mM, 100 mM, 500 mM, 1 M, 2 M, or 5M, or from about 0.1 mM to about 1 M, from about 0.1 mM to about 500 mM, from about 0.1 mM to about 250 mM, or from about 0.1 mM to about 100 mM.

The lipid particles and compositions described herein can further include an apolipoprotein. As used herein, the term "apolipoprotein" or "lipoprotein" refers to apolipoproteins known to those of skill in the art and variants and fragments thereof and to apolipoprotein agonists, analogues or fragments thereof described below.

In a preferred embodiment, the active agent is a nucleic acid, such as a siRNA. For example, the active agent can be a nucleic acid encoded with a product of interest, including but not limited to, RNA, antisense oligonucleotide, an antagomir, a DNA, a plasmid, a ribosomal RNA (rRNA), a micro RNA (miRNA) (e.g., a miRNA which is single stranded and 17-25 nucleotides in length), transfer RNA (tRNA), a small interfering RNA (siRNA), small nuclear RNA (snRNA), antigens, fragments thereof, proteins, peptides, vaccines and small molecules or mixtures thereof. In one more preferred embodiment, the nucleic acid is an oligonucleotide (e.g., 15-50 nucleotides in length (or 15-30 or 20-30 nucleotides in length)). An siRNA can have, for instance, a duplex region that is 16-30 nucleotides long. In another embodiment, the nucleic acid is an immunostimulatory oligonucleotide, decoy oligonucleotide, supermir, miRNA mimic, or miRNA inhibitor. A supermir refers to a single stranded, double stranded or partially double stranded oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or both or modifications thereof, which has a nucleotide sequence that is substantially identical to an miRNA and that is antisense with respect to its target. miRNA mimics represent a class of molecules that can be used to imitate the gene silencing ability of one or more miRNAs. Thus, the term "microRNA mimic" refers to synthetic non-coding RNAs (i.e. the miRNA is not obtained by purification from a source of the endogenous miRNA) that are capable of entering the RNAi pathway and regulating gene expression.

The nucleic acid that is present in a lipid-nucleic acid particle can be in any form. The nucleic acid can, for example, be single-stranded DNA or RNA, or double-stranded DNA or RNA, or DNA-RNA hybrids. Non-limiting examples of double-stranded RNA include siRNA. Single-stranded nucleic acids include, e.g., antisense oligonucle-

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otides, ribozymes, microRNA, and triplex-forming oligonucleotides. The lipid particles of the present invention can also deliver nucleic acids which are conjugated to one or more ligands.

5 Pharmaceutical Compositions

The lipid particles, particularly when associated with a therapeutic agent, may be formulated as a pharmaceutical composition, e.g., which further comprises a pharmaceutically acceptable diluent, excipient, or carrier, such as physiological saline or phosphate buffer.

The resulting pharmaceutical preparations may be sterilized by conventional, well known sterilization techniques. The aqueous solutions can then be packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, and tonicity adjusting agents, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, and calcium chloride. Additionally, the lipidic suspension may include lipid-protective agents which protect lipids against free-radical and lipid-peroxidative damages on storage. Lipophilic free-radical quenchers, such as α -tocopherol and water-soluble iron-specific chelators, such as ferrioxamine, are suitable.

The concentration of lipid particle or lipid-nucleic acid particle in the pharmaceutical formulations can vary, for example, from less than about 0.01%, to at or at least about 0.05-5% to as much as 10 to 30% by weight.

30 Methods of Manufacture

Methods of making cationic lipids, lipid particles containing them, and pharmaceutical compositions containing the cationic lipids and/or lipid particles are described in, for example, International Publication Nos. WO 2010/054406, WO 2010/054401, WO 2010/054405, WO 2010/054384, WO 2010/042877, WO 2010/129709, WO 2009/086558, and WO 2008/042973, and U.S. Patent Publication Nos. 2004/0142025, 2006/0051405 and 2007/0042031, each of which is incorporated by reference in its entirety.

For example, in one embodiment, a solution of one or more lipids (including a cationic lipid of any of the embodiments described herein) in an organic solution (e.g., ethanol) is prepared. Similarly, a solution of one or more active (therapeutic) agents (such as, for example an siRNA molecule or a 1:1 molar mixture of two siRNA molecules) in an aqueous buffered (e.g., citrate buffer) solution is prepared. The two solutions are mixed and diluted to form a colloidal suspension of siRNA lipid particles. In one embodiment, the siRNA lipid particles have an average particle size of about 80-90 nm. In further embodiments, the dispersion may be filtered through 0.45/2 micron filters, concentrated and diafiltered by tangential flow filtration.

Definitions

As used herein, the term "cationic lipid" includes those lipids having one or two fatty acid or fatty aliphatic chains and an amino acid containing head group that may be protonated to form a cationic lipid at physiological pH. In some embodiments, a cationic lipid is referred to as an "amino acid conjugate cationic lipid."

A subject or patient in whom administration of the complex is an effective therapeutic regimen for a disease or disorder is preferably a human, but can be any animal, including a laboratory animal in the context of a clinical trial or screening or activity experiment. Thus, as can be readily

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appreciated by one of ordinary skill in the art, the methods, compounds and compositions of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to, humans, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, and cats, avian species, such as chickens, turkeys, and songbirds, i.e., for veterinary medical use.

Many of the chemical groups recited in the generic formulas above are written in a particular order (for example, $-\text{OC}(\text{O})-$). It is intended that the chemical group is to be incorporated into the generic formula in the order presented unless indicated otherwise. For example, a generic formula of the form $-(\text{R})_i-(\text{M}^1)_k-(\text{R})_m-$ where M^1 is $-\text{C}(\text{O})\text{O}-$ and k is 1 refers to $-(\text{R})_i-\text{C}(\text{O})\text{O}-(\text{R})_m-$ unless specified otherwise. It is to be understood that when a chemical group is written in a particular order, the reverse order is also contemplated unless otherwise specified. For example, in a generic formula $-(\text{R})_i-(\text{M}^1)_k-(\text{R})_m-$ where M^1 is defined as $-\text{C}(\text{O})\text{NH}-$ (i.e., $-(\text{R})_i-\text{C}(\text{O})\text{NH}-(\text{R})_m-$), the compound where M^1 is $-\text{NHC}(\text{O})-$ (i.e., $-(\text{R})_i-\text{NHC}(\text{O})-(\text{R})_m-$) is also contemplated unless otherwise specified.

The term “biodegradable cationic lipid” refers to a cationic lipid having one or more biodegradable groups located in the mid- or distal section of a lipidic moiety (e.g., a hydrophobic chain) of the cationic lipid. The incorporation of the biodegradable group(s) into the cationic lipid results in faster metabolism and removal of the cationic lipid from the body following delivery of the active pharmaceutical ingredient to a target area.

As used herein, the term “biodegradable group” refers to a group that include one or more bonds that may undergo bond breaking reactions in a biological environment, e.g., in an organism, organ, tissue, cell, or organelle. For example, the biodegradable group may be metabolizable by the body of a mammal, such as a human (e.g., by hydrolysis). Some groups that contain a biodegradable bond include, for example, but are not limited to esters, dithiols, and oximes. Non-limiting examples of biodegradable groups are $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{SC}(\text{O})-$, $-\text{C}(\text{O})\text{S}-$, $-\text{OC}(\text{S})-$, $-\text{C}(\text{S})\text{O}-$, $-\text{S}-\text{S}-$, $-\text{C}(\text{R}^5)=\text{N}-$, $-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^5)=\text{N}-\text{O}-$, $-\text{O}-\text{N}=\text{C}(\text{R}^5)-$, $-\text{C}(\text{O})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{C}(\text{S})(\text{NR}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})\text{N}(\text{R}^5)-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{OSi}(\text{R}^5)_2\text{O}-$, $-\text{C}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})\text{O}-$, or $-\text{OC}(\text{O})(\text{CR}^3\text{R}^4)\text{C}(\text{O})-$.

As used herein, an “aliphatic” group is a non-aromatic group in which carbon atoms are linked into chains, and is either saturated or unsaturated.

The terms “alkyl” and “alkylene” refer to a straight or branched chain saturated hydrocarbon moiety. In one embodiment, the alkyl group is a straight chain saturated hydrocarbon. Unless otherwise specified, the “alkyl” or “alkylene” group contains from 1 to 24 carbon atoms. Representative saturated straight chain alkyl groups include methyl, ethyl, n-propyl, n-butyl, n-pentyl, and n-hexyl. Representative saturated branched alkyl groups include isopropyl, sec-butyl, isobutyl, tert-butyl, and isopentyl.

The term “alkenyl” refers to a straight or branched chain hydrocarbon moiety having one or more carbon-carbon double bonds. In one embodiment, the alkenyl group contains 1, 2, or 3 double bonds and is otherwise saturated. Unless otherwise specified, the “alkenyl” group contains from 2 to 24 carbon atoms. Alkenyl groups include both cis

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and trans isomers. Representative straight chain and branched alkenyl groups include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, and 2,3-dimethyl-2-butenyl.

The term “alkynyl” refers to a straight or branched chain hydrocarbon moiety having one or more carbon-carbon triple bonds. Unless otherwise specified, the “alkynyl” group contains from 2 to 24 carbon atoms. Representative straight chain and branched alkynyl groups include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, and 3-methyl-1-butyne.

Unless otherwise specified, the terms “branched alkyl”, “branched alkenyl”, and “branched alkynyl” refer to an alkyl, alkenyl, or alkynyl group in which one carbon atom in the group (1) is bound to at least three other carbon atoms and (2) is not a ring atom of a cyclic group. For example, a spirocyclic group in an alkyl, alkenyl, or alkynyl group is not considered a point of branching.

Unless otherwise specified, the term “acyl” refers to a carbonyl group substituted with hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, or heteroaryl. For example, acyl groups include groups such as $(\text{C}_1-\text{C}_{20})$ alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, and t-butylacetyl), $(\text{C}_3-\text{C}_{20})$ cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, and cyclohexylcarbonyl), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolidin-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, and tetrahydrofuranylcarbonyl), aroyl (e.g., benzoyl) and heteroaroaryl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrrolyl-2-carbonyl, 1H-pyrrolyl-3-carbonyl, and benzo[b] thiophenyl-2-carbonyl).

The term “aryl” refers to an aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Unless otherwise specified, the “aryl” group contains from 6 to 14 carbon atoms. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, anthracenyl, and pyrenyl.

The terms “cycloalkyl” and “cycloalkylene” refer to a saturated monocyclic or bicyclic hydrocarbon moiety such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Unless otherwise specified, the “cycloalkyl” or “cycloalkylene” group contains from 3 to 10 carbon atoms.

The term “cycloalkylalkyl” refers to a cycloalkyl group bound to an alkyl group, where the alkyl group is bound to the rest of the molecule.

The term “heterocycle” (or “heterocyclyl”) refers to a non-aromatic 5- to 8-membered monocyclic, or 7- to 12-membered bicyclic, or 11- to 14-membered tricyclic ring system which is either saturated or unsaturated, and which contains from 1 to 3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. For instance, the heterocycle may be a cycloalkoxy group. The heterocycle may be attached to the rest of the molecule via any heteroatom or carbon atom in the heterocycle. Heterocycles include, but are not limited to, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizynyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

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The term “heteroaryl” refers to an aromatic 5-8 membered monocyclic, 7-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, where the heteroatoms are selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively). The heteroaryl groups herein described may also contain fused rings that share a common carbon-carbon bond.

The term “substituted”, unless otherwise indicated, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, oxo, thioxy, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aryloxy carbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxy carbonylalkyl, aminocarbonylalkyl, acyl, aralkoxy carbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and an aliphatic group. It is understood that the substituent may be further substituted. Exemplary substituents include amino, alkylamino, dialkylamino, and cyclic amino compounds.

The term “halogen” or “halo” refers to fluoro, chloro, bromo and iodo.

The following abbreviations may be used in this application:

DSPC: distearoylphosphatidylcholine; DPPC: 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine; POPC: 1-palmitoyl-2-oleoyl-sn-phosphatidylcholine; DOPE: 1,2-dioleoyl-sn-3-

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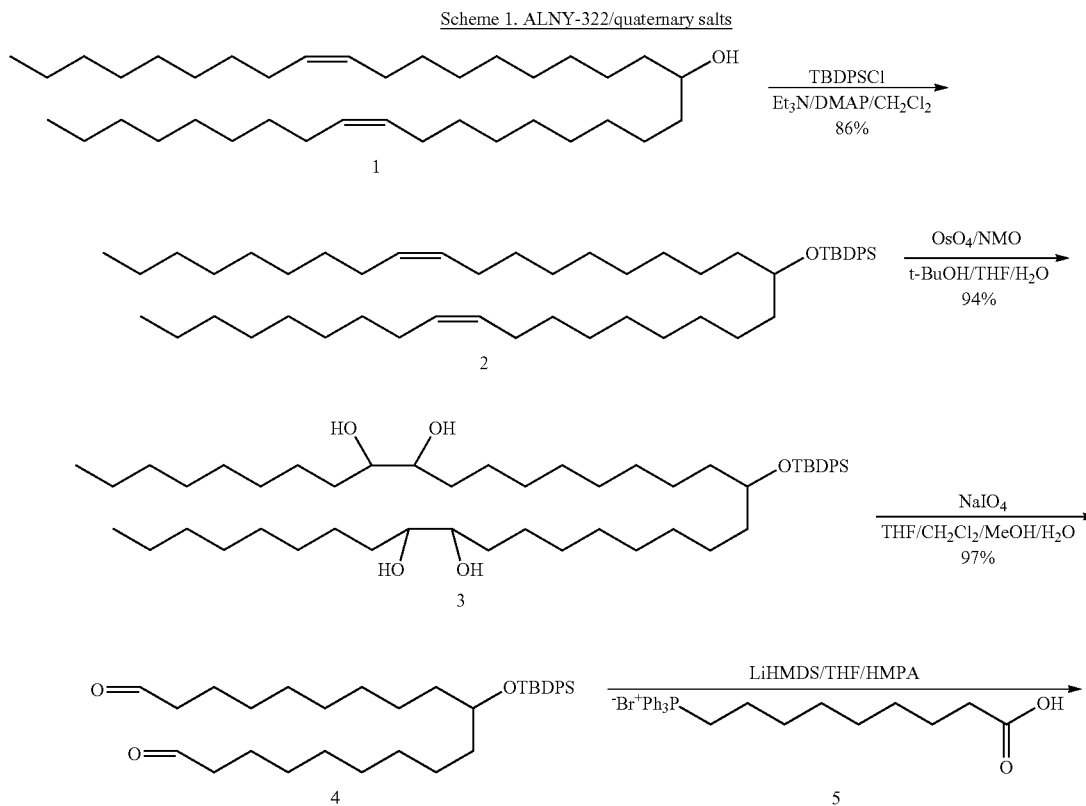
phosphoethanolamine; PEG-DMG generally refers to 1,2-dimyristoyl-sn-glycerol-methoxy polyethylene glycol (e.g., PEG 2000); TBDPSCI: tert-Butylchlorodiphenylsilane; DMAP: dimethylaminopyridine; HMPA: hexamethylphosphoramide; EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; DIPEA: diisopropylethylamine; DCM: dichloromethane; TEA: triethylamine; TBAF: tetrabutylammonium fluoride

Methods to prepare various organic groups and protective groups are known in the art and their use and modification is generally within the ability of one of skill in the art (see, for example, Green, T. W. et. al., *Protective Groups in Organic Synthesis* (1999); Stanley R. Sandler and Wolf Karo, *Organic Functional Group Preparations* (1989); Greg T. Hermanson, *Bioconjugate Techniques* (1996); and Leroy G. Wade, *Compendium Of Organic Synthetic Methods* (1980)). Briefly, protecting groups are any group that reduces or eliminates unwanted reactivity of a functional group. A protecting group can be added to a functional group to mask its reactivity during certain reactions and then removed to reveal the original functional group. In some embodiments an “alcohol protecting group” is used. An “alcohol protecting group” is any group which decreases or eliminates unwanted reactivity of an alcohol functional group. Protecting groups can be added and removed using techniques well known in the art.

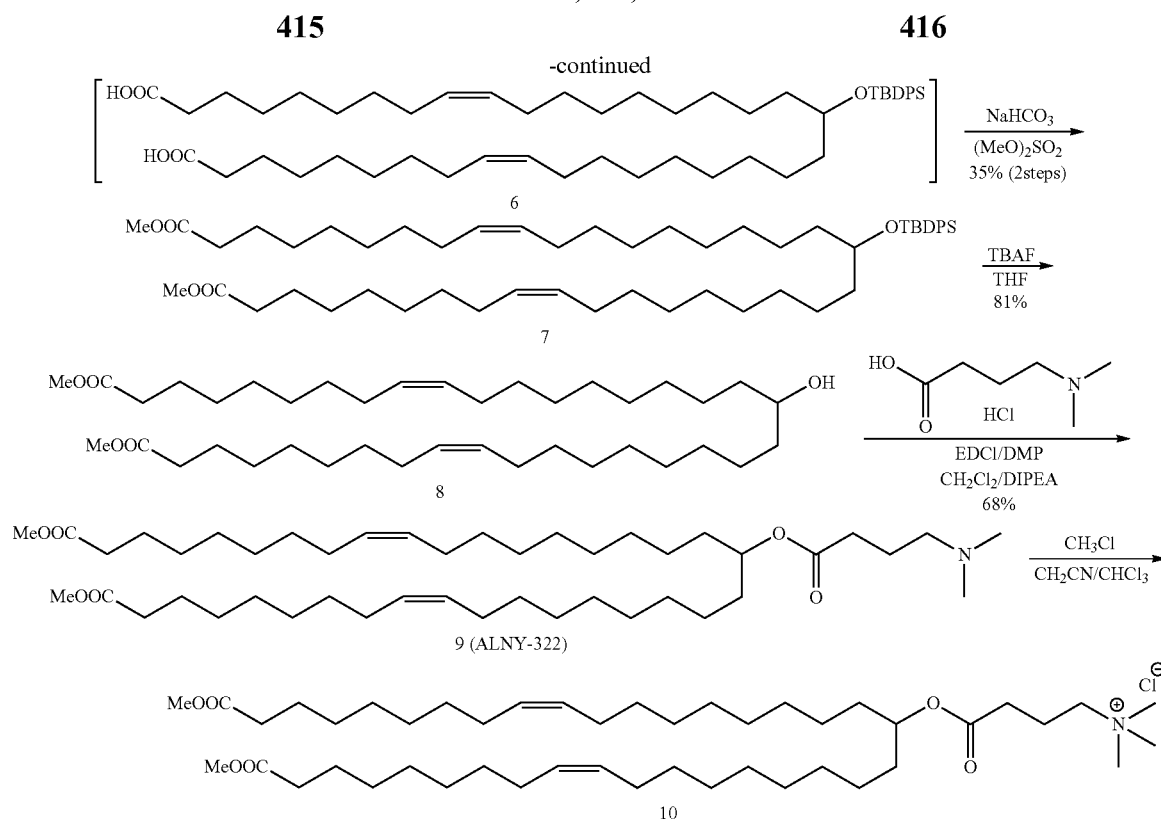
The compounds may be prepared by at least one of the techniques described herein or known organic synthesis techniques.

EXAMPLES

Example 1



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Compound 2: To a solution of compound 1 (10.0 g, 18.8 mmol, see International Publication No. WO 2010/054406) in CH_2Cl_2 (80 mL) were added triethylamine (7.86 mL, 56.4 mmol), DMAP (459 mg, 3.76 mmol) and tert-butyl(chloro) diphenylsilane (9.62 mL, 37.6 mmol). The reaction mixture was stirred for 24 hours. The mixture was then diluted with CH_2Cl_2 and washed with aqueous saturated NaHCO_3 solution. The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and concentration, the crude product was purified by silica gel column chromatography (0-5% EtOAc in hexane) to afford 2 (12.4 g, 16.1 mmol, 86%, R_f =0.24 with hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.66-7.68 (m, 4H), 7.33-7.42 (m, 6H), 5.30-5.39 (m, 4H), 3.67-3.72 (m, 1H), 1.97-2.04 (m, 8H), 1.07-1.42 (m, 52H), 1.05 (s, 9H), 0.88 (t, J =6.8 Hz, 6H).

Compound 3: To a solution of 2 (12.4 g, 16.1 mmol) in tert-butanol (100 mL), THF (30 mL) and H_2O (10 mL) were added 4-methylmorpholine N-oxide (4.15 g, 35.4 mmol) and osmium tetroxide (41 mg, 0.161 mg). The reaction mixture was stirred for 16 hours, then quenched by adding sodium bisulfite. After removing the solvents by evaporation, the residue was extracted with Et_2O (500 mL) and H_2O (300 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and concentration, the crude was purified by silica gel column chromatography (hexane: EtOAc=1:1, R_f =0.49) to afford 3 (12.7 g, 15.1 mmol, 94%). ^1H NMR (400 MHz, CDCl_3) δ 7.66-7.68 (m, 4H), 7.33-7.43 (m, 6H), 3.67-3.73 (m, 1H), 3.57-3.62 (m, 4H), 1.82 (t, J =5.0 Hz, 4H), 1.10-1.51 (m, 60H), 1.04 (s, 9H), 0.88 (t, J =6.8 Hz, 6H).

Compound 4: To a solution of 3 (12.6 g, 15.0 mmol) in 1,4-dioxane (220 mL), CH_2Cl_2 (70 mL), MeOH (55 mL), and H_2O (55 mL) was added NaIO_4 (7.70 g, 36.0 mmol). The reaction mixture was stirred for 16 hours at room temperature. The mixture was extracted with Et_2O (500 mL)

and H_2O (300 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and concentration, the crude product was purified by silica gel column chromatography (Hexane:EtOAc=9:1, R_f =0.30) to afford 4 (7.98 g, 14.5 mmol, 97%). Molecular weight for $\text{C}_{35}\text{H}_{54}\text{NaO}_3\text{Si}$ ($M+\text{Na}$) $^+$ Calc. 573.3740, Found 573.3.

Compound 7: To a solution of 5 (see, Tetrahedron, 63, 1140-1145, 2006; 1.09 g, 2.18 mmol) in THF (20 mL) and HMPA (4 mL), LiHMDS (1 M THF solution, 4.36 mL, 4.36 mmol) was added at -20°C . The resulting mixture was stirred for 20 minutes at the same temperature, then cooled to -78°C . A solution of 4 (500 mg, 0.908 mmol) in THF (4 mL) was added. The mixture was stirred and allowed to warm to room temperature overnight. MS analysis showed the formation of the di-acid (6; $\text{C}_{53}\text{H}_{85}\text{O}_5\text{Si}$ ($M-\text{H}$) $^-$ calc. 829.6166, observed 829.5). To the mixture, NaHCO_3 (1.10 g, 13.1 mmol) and dimethyl sulfate (1.24 mL, 13.1 mmol) were added and stirred for 2 hours at room temperature. The reaction was quenched by adding saturated NH_4Cl aqueous solution (50 mL) then extracted with Et_2O (2 \times 100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and concentration, the crude product was purified by silica gel column chromatography (Hexane: EtOAc=9:1, R_f =0.35) to afford 7 (270 mg, 0.314 mmol, 35%). Molecular weight for $\text{C}_{55}\text{H}_{90}\text{NaO}_5\text{Si}$ ($M+\text{Na}$) $^+$ Calc. 881.6455, Found 881.6484.

Compound 8: To a solution of 7 (265 mg, 0.308 mmol) in THF (2.5 mL), n-TBAF (1 M THF solution, 0.555 mL, 0.555 mmol) was added. The reaction mixture was stirred for 14 hours at 45°C . After concentration, the mixture was purified by silica gel column chromatography (Hexane: EtOAc=3:1, R_f =0.52) to afford 8 (155 mg, 0.250 mmol, 81%). Molecular weight for $\text{C}_{39}\text{H}_{72}\text{NaO}_5$ ($M+\text{Na}$) $^+$ Calc. 643.5277, Found 643.5273.

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Compound 9: To a solution of compound 8 (150 mg, 0.242 mmol) and 4-(dimethylamino)butyric acid hydrochloride (49 mg, 0.290 mmol) in CH_2Cl_2 (5 mL) were added diisopropylethylamine (0.126 mL, 0.726 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (56 mg, 0.290 mmol) and DMAP (6 mg, 0.0484 mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with saturated NaHCO_3 aq. (50 mL). The organic layer was dried over MgSO_4 , filtered and

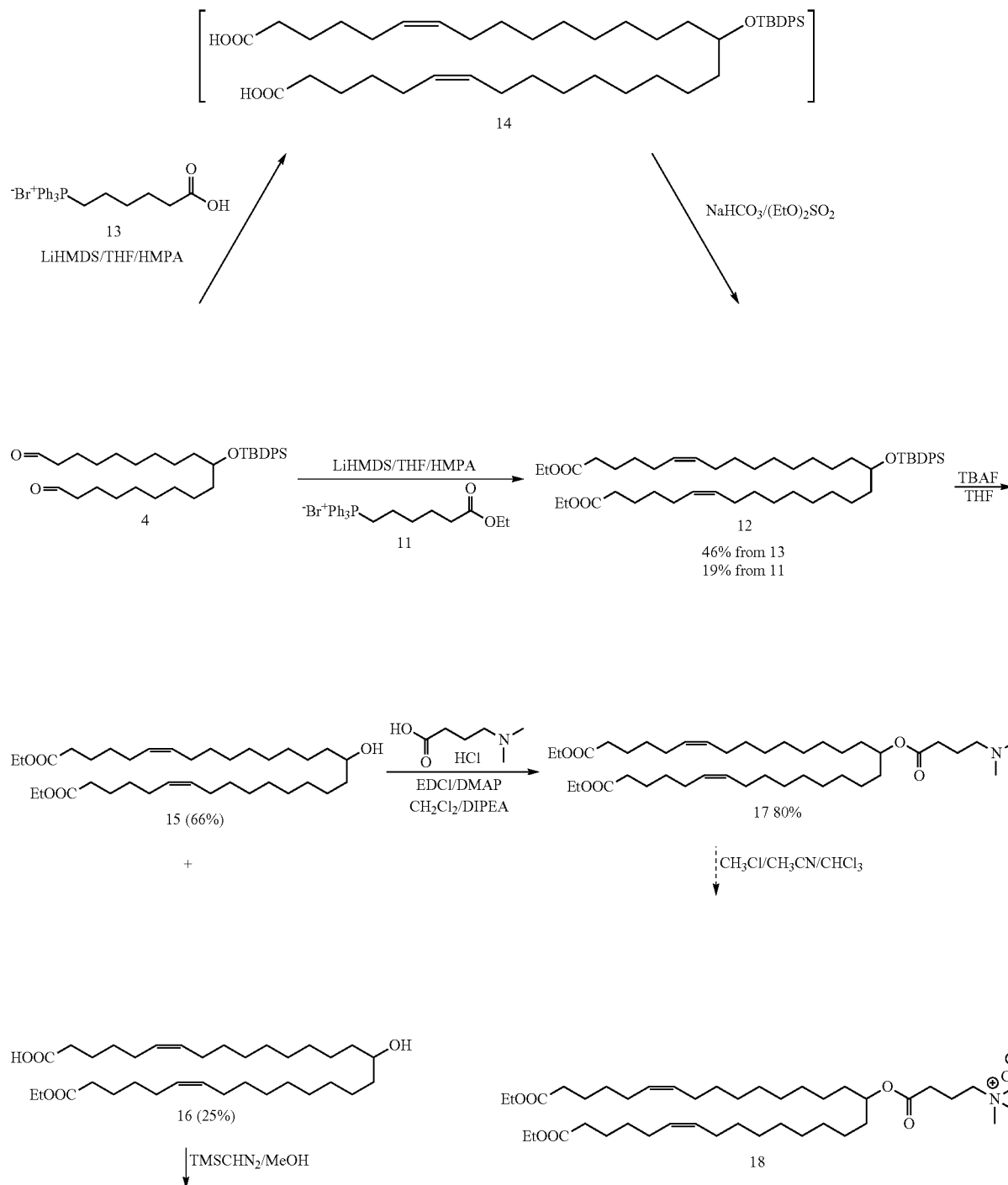
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concentrated. The crude product was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to afford compound 9 (121 mg, 0.165 mmol, 68%, $R_f=0.25$ developed with 5% MeOH in CH_2Cl_2). Molecular weight for $\text{C}_{45}\text{H}_{84}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 734.6299, Found 734.5.

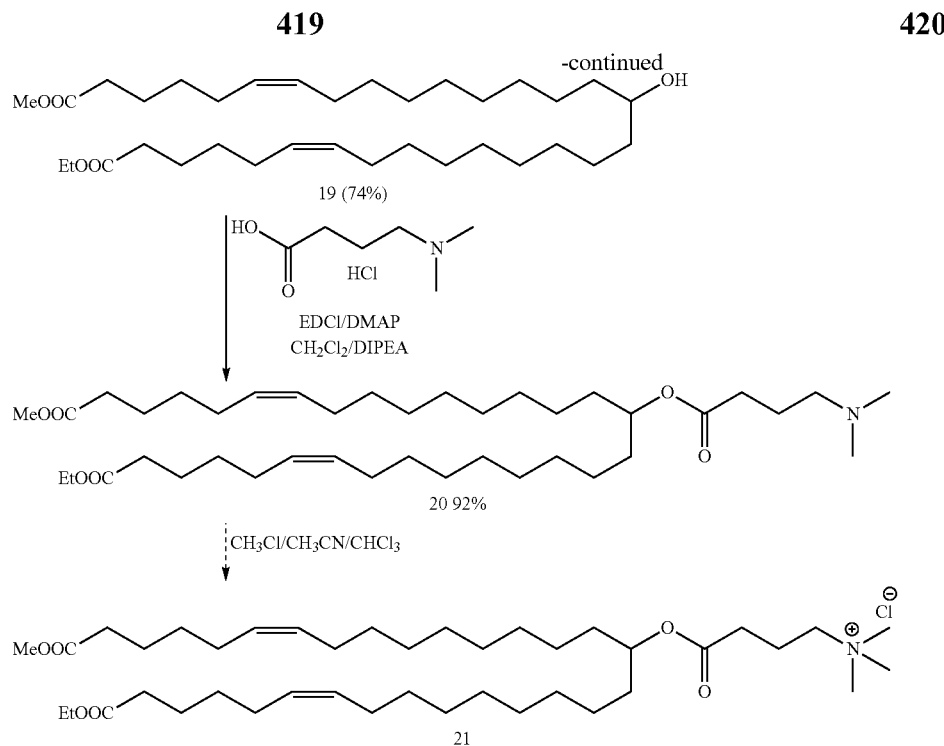
Compound 10: Treatment of compound 9 with CH_3Cl in CH_3CN and CHCl_3 can afford compound 10.

Example 2

Scheme 2



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Compound 12: To a solution of 11 (Journal of Medicinal Chemistry (1995), 38, 636-46; 1.25 g, 2.58 mmol) in THF (20 mL) and HMPA (4 mL), LiHMDS (1 M THF solution, 2.58 mL, 2.58 mmol) was added at -20°C . The mixture was stirred for 20 min at the same temperature, then cooled to -78°C . A solution of 4 (500 mg, 0.908 mmol) in THF (9 mL) and HMPA (0.9 mL) was added. The mixture was stirred from -78°C to room temperature overnight. The reaction was quenched by adding H_2O (40 mL) then extracted with Et_2O (150 mL \times 3). The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and concentration, the crude was purified by silica gel column chromatography (Hexane:EtOAc=9:1, R_f =0.35) to give 12 (136 mg, 0.169 mmol, 19%). Molecular weight for $\text{C}_{51}\text{H}_{82}\text{NaO}_5\text{Si}$ ($\text{M}+\text{Na}$) $^{+}$ Calc. 825.5829, Found 825.5.

Using 13 in place of 5, a procedure analogous to that described for compound 7 was followed to afford compound 12 (135 mg, 0.168 mmol, 46%).

Compound 15/Compound 16: To a solution of 12 (800 mg, 0.996 mmol) in THF (5 mL), n -TBAF (1 M THF solution, 5 mL, 5.00 mmol) was added. The reaction mixture was stirred for 16 h at 45°C . After concentration, the mixture was purified by silica gel column chromatography to give 15 (Hexane:EtOAc=3:1, R_f =0.46, 372 mg, 0.659 mmol, 66%) and 16 (CH_2Cl_2 :MeOH=95:5, R_f =0.36, 135 mg, 0.251 mmol, 25%). Molecular weight for 15; $\text{C}_{35}\text{H}_{64}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^{+}$ Calc. 587.4651, Found 587.4652. Molecular weight for 16; $\text{C}_{33}\text{H}_{61}\text{O}_5$ ($\text{M}+\text{H}$) $^{+}$ Calc. 537.4519, Found 537.5.

Compound 17: To a solution of compound 15 (164 mg, 0.290 mmol) and 4-(dimethylamino)butyric acid hydrochloride (58 mg, 0.348 mmol) in CH_2Cl_2 (5 mL) were added diisopropylethylamine (0.152 mL, 0.870 mmol), N -(3-dimethylaminopropyl)- N' -ethylcarbodiimide hydrochloride (67 mg, 0.348 mmol) and DMAP (7 mg, 0.058 mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with CH_2Cl_2 (100

mL) and washed with saturated NaHCO_3 aq. (50 mL). The organic layer was dried over MgSO_4 , filtered and concentrated. The crude was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give compound 17 (158 mg, 0.233 mmol, 80%, R_f =0.24 developed with 5% MeOH in CH_2Cl_2). Molecular weight for $\text{C}_{45}\text{H}_{84}\text{NO}_6$ ($\text{M}+\text{H}$) $^{+}$ Calc. 734.6299, Found 734.5.

Compound 18: Treatment of compound 17 with CH_3Cl in CH_3CN and CHCl_3 can afford compound 18.

Compound 19: To a solution of 16 (130 mg, 0.242 mmol) in THF (2 mL) and MeOH (2 mL), trimethylsilyldiazomethane (2 M solution in Et_2O , 0.158 mL, 0.315 mmol) was added. The reaction mixture was stirred for 14 h. After evaporation, the residue was purified by silica gel column chromatography (Hexane:EtOAc=3:1, R_f =0.50) to give 19 (99 mg, 0.180 mmol, 74%). ^1H NMR (400 MHz, CDCl_3) δ 5.29-5.40 (m, 4H), 4.12 (q, J =7.1 Hz, 2H), 3.66 (s, 3H), 3.55-3.59 (m, 1H), 2.30 (dd, J =14.7, 7.2 Hz, 4H), 1.98-2.07 (m, 8H), 1.60-1.68 (m, 4H), 1.23-1.43 (m, 37H).

Compound 20: To a solution of compound 19 (95 mg, 0.168 mmol) and 4-(dimethylamino)butyric acid hydrochloride (42 mg, 0.252 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (0.088 mL, 0.504 mmol), N -(3-dimethylaminopropyl)- N' -ethylcarbodiimide hydrochloride (48 mg, 0.504 mmol) and DMAP (4 mg, 0.034 mmol). The reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated NaHCO_3 aq. (50 mL). The organic layer was dried over MgSO_4 , filtered and concentrated. The crude was purified by silica gel column chromatography (0-5% MeOH in CH_2Cl_2) to give compound 20 (103 mg, 0.155 mmol, 92%, R_f =0.19 developed with 5% MeOH in CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 5.29-5.40 (m, 4H), 4.83-4.89 (m, 1H), 4.12 (q, J =7.1 Hz, 2H), 3.67 (s, 3H), 2.28-2.34 (m, 8H), 2.23 (s, 6H), 1.98-2.07 (m, 8H), 1.76-1.83 (m, 2H), 1.60-1.68 (m, 4H), 1.23-1.51 (m, 35H).

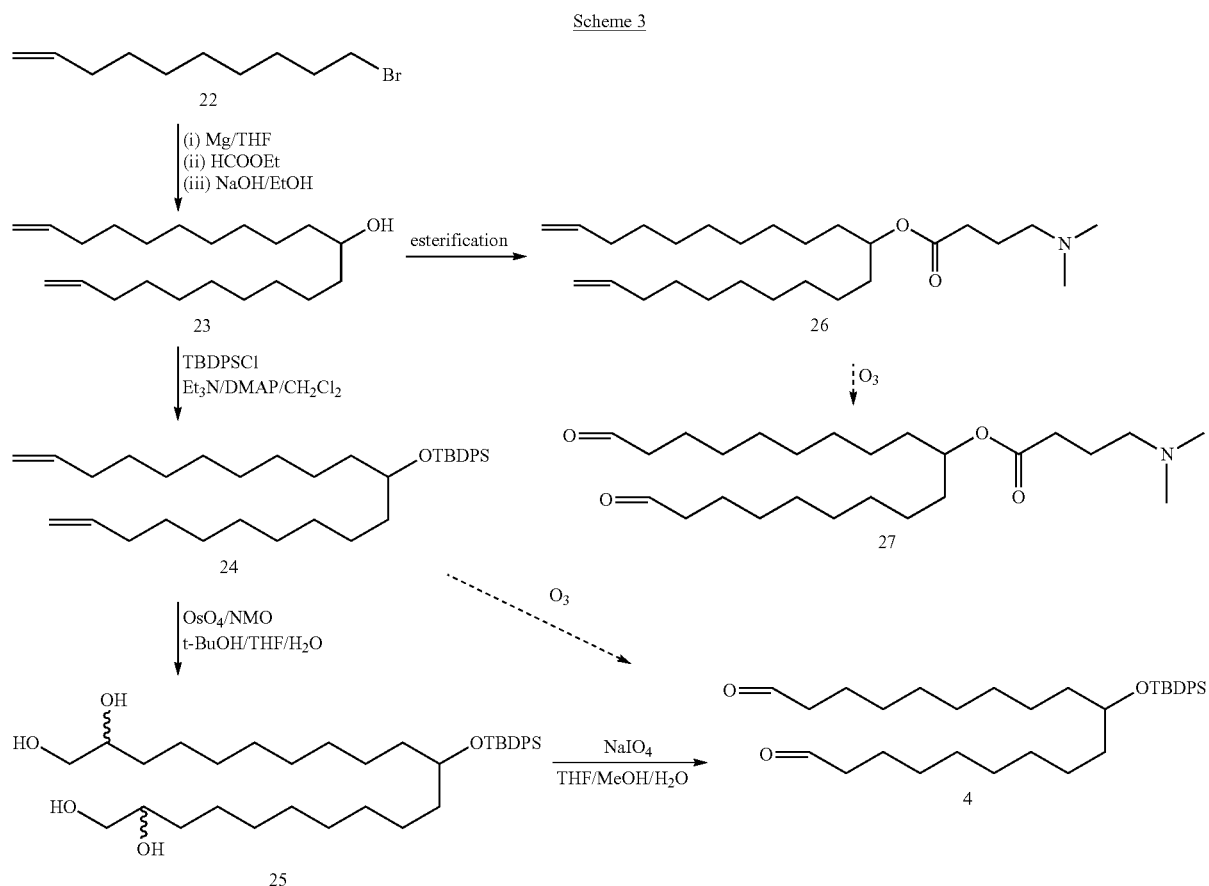
Compound 21: Treatment of compound 20 with CH_3Cl in CH_3CN and CHCl_3 can afford compound 21.

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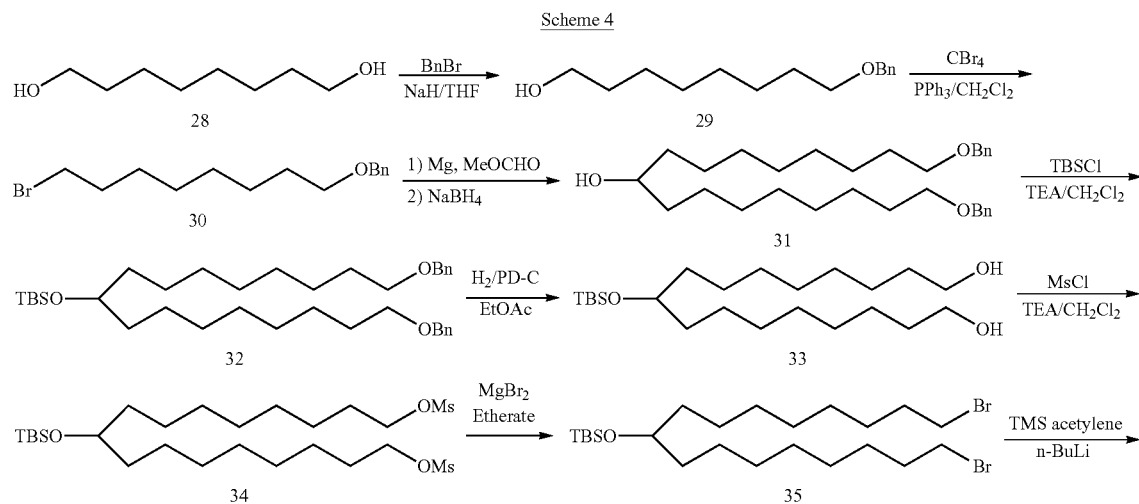
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Example 3: Alternate Synthesis for Di-Aldehyde Intermediate 4

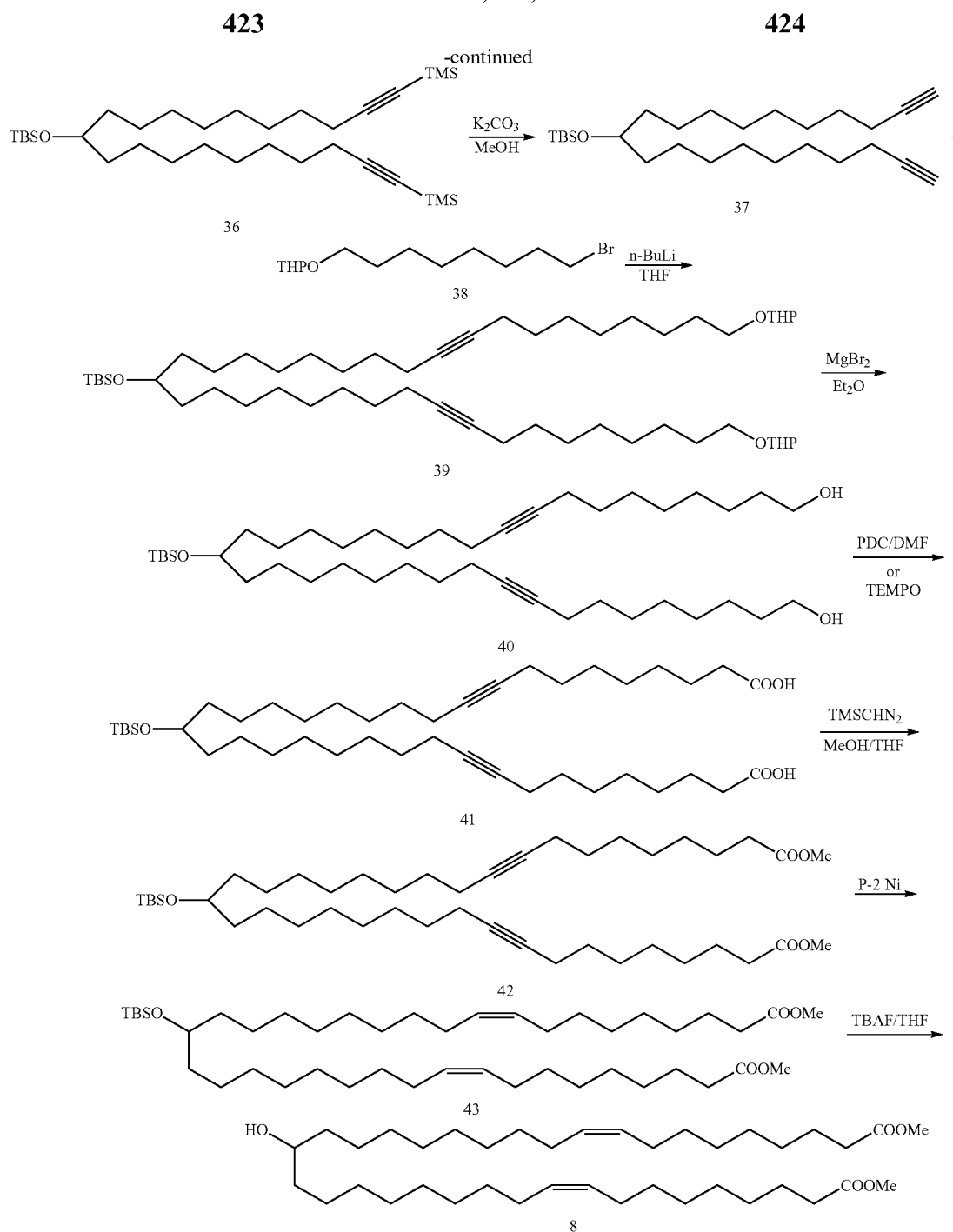


The di-aldehyde 4 can be synthesized as shown in Scheme 40 3, using 1-bromo-9-decene. Di-aldehyde containing a head group 27 can be useful for the synthesis of terminal ester-substituted lipids using, e.g., a Wittig reaction. Ozonolysis can afford di-aldehyde 4 and 27.

Example 4: Alternate Synthesis for Compound 8



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Compound 8 can be synthesized as shown in Scheme 4. 55

Compound 29: To a stirred suspension of NaH (60% in oil, 82 g, 1.7096 mol) in 500 mL anhydrous DMF, a solution of compound 28 (250 g, 1.7096 mol) in 1.5 L DMF was added slowly using a dropping funnel at 0° C. The reaction mixture was stirred for 30 minutes, then benzyl bromide 60 (208.86 mL, 1.7096 mol) was added slowly under an atmosphere of nitrogen. The reaction was then warmed to ambient temperature and stirred for 10 hours. The mixture was then quenched with crushed ice (~2 kg) and extracted with ethyl acetate (2×1 L). The organic layer was washed with water (1 L) to remove unwanted DMF, dried over Na₂SO₄ 65 and evaporated to dryness in vacuo. The crude compound was purified on 60-120 silica gel, eluted with 0-5% MeOH in DCM to afford compound 29 (220 g, 54%) as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 5H), 4.49 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 1.63-1.51 (m, 4H), 1.39-1.23 (m, 8H).

Compound 30: Compound 29 (133 g, 0.5635 mol) was dissolved in 1.5 L of DCM, CBr₄ (280.35 g, 0.8456 mol) was added into this stirring solution and the reaction mixture was cooled to 0° C. under an inert atmosphere. PPh₃ (251.03 g, 0.9571 mol) was then added in portions keeping the temperature below 20° C. After complete addition, the reaction mixture was stirred for 3 hours at room temperature. After completion of the reaction, the solid (PPh₃O) that precipi-

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tated from the reaction mixture was removed by filtration, and the filtrate was diluted with crushed ice (~1.5 kg) and extracted with DCM (3×750 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and distilled under vacuum. The resulting crude compound was chromatographed on 60-120 mesh silica gel column using 0-5% ethyl acetate in hexanes as eluting system to afford compound 30 (150 g, 89%) as pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.47-3.41 (m, 2H), 3.41-3.37 (m, 2H), 1.86-1.80 (m, 4H), 1.62-1.56 (m, 2H), 1.42-1.29 (m, 8H).

Compound 31: To freshly activated Mg turnings (24.08 g, 1.003 mol) was added 200 mL anhydrous THF, followed by the addition of pinch of iodine into the mixture under an inert atmosphere. A solution of Compound 30 (150 g, 0.5016 mol) in 1 L of dry THF was added slowly, controlling the exothermic reaction. The reaction was then heated to reflux for 1 hour, then cooled to room temperature. Methyl formate (60.24 g, 1.0033 mol) was then added slowly and the reaction was continued for 2 hours. After completion, the reaction was quenched by slow addition of 10% HCl followed by water (1 L) and extracted with ethyl acetate (3×1 L). The organic layer was taken in 5 litre beaker, diluted with 500 mL of methanol and cooled to 0° C. To this solution, an excess of NaBH₄ (~5 eq) was added in portions to ensure hydrolysis of the formate ester which was not cleaved by addition of HCl. The resulting solution was stirred for an hour and then volatiles were removed under vacuum. The residue was taken in water (1 L) and acidified by 10% HCl solution (pH 4). The product was then extracted with ethyl acetate (3×1 L). The organic phase was then dried and concentrated on rotary evaporator to afford the desired compound 31 (57 g, 24%) as solid. ¹H NMR (400 MHz, CDCl₃): δ=7.35-7.32 (m, 8H), 7.29-7.24 (m, 2H), 4.49 (s, 4H), 3.56 (m, 1H), 3.46-3.43 (m, 4H), 1.63-1.56 (m, 4H), 1.44-1.34 (m, 28H). ¹³C NMR (100 MHz, CDCl₃): δ=138.56, 128.21, 127.49, 127.34, 72.72, 71.76, 70.37, 37.37, 29.64, 29.56, 29.47, 29.33, 26.07, 25.54.

Compound 32: Compound 31 (56 g, 0.1196 mol) was dissolved in 700 mL dry THF and cooled to 0° C. TBSCl (36.06 g, 0.2396 mol) was added slowly followed by the addition of imidazole (32.55 g, 0.4786 mol) under an inert atmosphere. The reaction was then stirred at room temperature for 18 hours. Upon completion, the reaction was quenched with ice (~1 kg) and extracted with ethyl acetate (3×500 mL). The organic layer was separated, washed with saturated NaHCO₃ solution to remove acidic impurities, dried over Na₂SO₄ and evaporated under reduce pressure to afford a crude compound that was purified by silica gel (60-120 mesh) and eluted with 0-10% ethyl acetate hexane to afford (60 g, 82%) of compound 32 as yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 10H), 4.49 (s, 4H), 3.60-3.57 (m, 1H), 3.46-3.43 (m, 4H), 1.61-1.54 (m, 4H), 1.41-1.26 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H).

Compound 33: Compound 32 (60 g, 0.1030 mol) was dissolved in 500 mL ethyl acetate and degassed with N₂ for 20 minutes. (10 wt %) Pd on carbon (12 g) was added and the reaction was stirred under an atmosphere of hydrogen for 18 hours. After completion, the mixture was filtered through a bed of celite and washed with ethyl acetate. The filtrate was evaporated under vacuum to afford compound 33 (19 g, 46%) that was pure enough to use in the next synthetic sequence. ¹H NMR (400 MHz, CDCl₃): δ=3.64-3.58 (m, 5H), 1.59 (br, 2H), 1.57-1.51 (m, 4H), 1.38-1.22 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H).

Compound 34: Compound 33 (8.2 g, 0.0199 mol) was dissolved in 100 mL dry DCM and cooled to 0° C. TEA

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(22.14 mL, 0.1592 mol) was added under an inert atmosphere. After stirring the mixture for 5 minutes, mesyl chloride (4.6 mL, 0.059 mol) was added drop wise and the reaction was stirred further for 3 hours. After completion of the reaction, the mixture was quenched with ice (~200 g) and extracted with DCM (3×75 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford a crude compound which was purified on a 60-120 mesh silica gel column using 0-30% ethyl acetate in hexane as eluting system to afford compound 34 (8.2 g, 73%) as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=4.22-4.19 (m, 4H), 3.60-3.58 (m, 1H), 2.99 (s, 6H), 1.75-1.69 (m, 4H), 1.38-1.28 (m, 28H), 0.86 (s, 9H), 0.02 (s, 6H).

Compound 35: To a solution of compound 34 (8.2 g, 0.0146 mol) in 400 mL dry ether was added MgBr₂·Et₂O (22.74 g, 0.08817 mol) in portions at 0° C. under a nitrogen atmosphere. After complete addition, the reaction mixture was heated to reflux for 28 hours. After completion of reaction, inorganic material formed in the reaction was removed by filtration. The filtrate was evaporated and the resulting crude compound was purified on 60-120 mesh silica gel column using 0-3% ethyl acetate in hexanes as eluting system to afford compound 35 (6.6 g, 85%) as a colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ=3.61-3.58 (m, 1H), 3.41-3.37 (t, 4H, J=6.8 Hz), 1.87-1.80 (m, 4H), 1.42-1.25 (m, 24H), 0.87 (s, 9H), 0.012 (s, 6H).

Compound 36: A solution of ethynyl trimethyl silane (5.3 mL, 0.0378 mol) in 60 mL dry THF was cooled to -78° C. and 1.4 M n-BuLi (23 mL, 0.03405 mol) in hexane was added slowly under an inert atmosphere. The reaction was stirred for 10 minutes, then HMPA (2.3 g, 0.01324 mol) was added and the resulting mixture was then stirred for 2 hours at 0° C., then cooled to -78° C. To this a solution of compound 35 (5 g, 0.0094 mol) in 60 mL dry THF was added slowly and after complete addition, the reaction was warmed to room temperature and maintained for 18 hours. The reaction progress was monitored by ¹H NMR. After completion, the reaction mixture was cooled to 0° C. and quenched by careful addition of saturated NH₄Cl solution (50 mL) followed by water (200 mL). The aqueous phase was extracted with hexane (3×250 mL). The organic layer was dried and solvent removed under vacuum to afford compound 36 (5 g, 94%), which was used without further purification. ¹H NMR (400 MHz, CDCl₃): δ=3.62-3.56 (m, 1H), 2.21-2.17 (m, 4H), 1.49-1.47 (m, 4H), 1.37-1.26 (m, 24H), 0.87 (s, 9H), 0.13 (s, 18H), 0.021 (s, 6H).

Compound 37: To a stirred solution of compound 36 (5 g, 0.0088 mol) in 50 mL methanol, was added K₂CO₃ (6.1 g, 0.044 mol) in one portion, and the resulting mixture was stirred for 18 hours at ambient temperature. Volatilities were then removed on a rotary evaporator and the crude mixture was diluted with 100 mL water and extracted with hexane (3×100 mL). The organic layer was dried over Na₂SO₄ and evaporated under vacuum to afford compound 37 (3.5 g, 97%) which was used which was used without further purification. ¹H NMR (400 MHz, CDCl₃): δ=3.60-3.58 (m, 1H), 2.19-2.14 (m, 4H), 1.93-1.92 (m, 2H), 1.54-1.49 (m, 4H), 1.37-1.27 (m, 24H), 0.87 (s, 9H), 0.02 (s, 6H).

Compound 39: Compound 37 (2.5 g, 0.00598 mol) was dissolved in 25 mL dry THF and cooled to -40° C. n-BuLi (1.4 M in hexane 12.9 mL, 0.01794 mol) was added slowly, followed, after a 10 minute interval, by slow addition of HMPA (25 mL). The resulting mixture was maintained for 30 minutes -40° C. under a nitrogen atmosphere. A solution of compound 38 (3.5 g, 1.01196 mol) in 25 mL dry THF was then added drop wise to the cooled reaction mixture. The resulting mixture was warmed to room temperature over 2

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hours, then stirred at room temperature for 18 hours. The mixture was then quenched by adding saturated NH_4Cl solution (~50 mL) and the product was extracted with ethyl acetate (3x50 mL). The solvent was removed on a rotary evaporator and the resulting crude product was purified by (100-200 mesh) silica gel column using 0-3% ethyl acetate in dichloromethane as eluting system to afford compound 39 (0.9 g, 18%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ =4.56-4.55 (m, 2H), 3.87-3.83 (m, 2H), 3.74-3.68 (m, 2H), 3.59-3.57 (m, 1H), 3.49-3.46 (m, 2H), 3.39-3.33 (m, 2H), 2.13-2.10 (m, 8H), 1.87-1.75 (m, 2H), 1.74-1.66 (m, 2H), 1.57-1.42 (m, 20H), 1.40-1.19 (m, 40H), 0.87 (s, 9H), 0.02 (s, 6H).

Compound 40: To a solution of compound 39 (504 mg, 0.598 mmol) in 10 mL dry ether was added $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ (926 mg, 3.59 mmol). The reaction mixture was stirred for 14 hours, then quenched by adding saturated NaHCO_3 aqueous solution. The product was extracted with CH_2Cl_2 . The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography to afford compound 40 (307 mg, 0.455 mmol, 76%, R_f =0.36 developed with hexane:EtOAc=2:1). ^1H NMR (400 MHz, CDCl_3) δ 3.59-3.66 (m, 5H), 2.14 (t, J =6.6 Hz, 8H), 1.21-1.59 (m, 52H), 0.88 (s, 9H), 0.03 (s, 6H).

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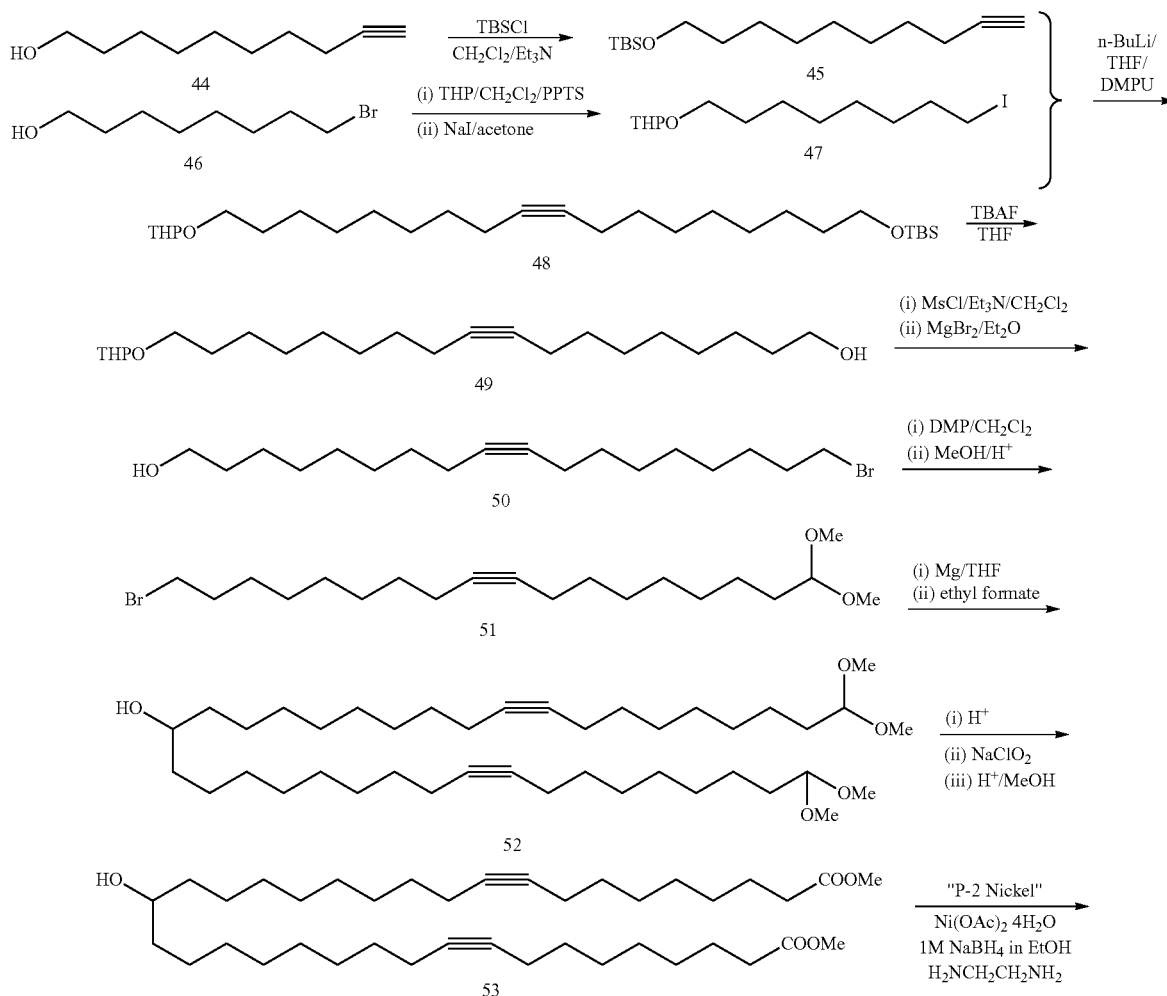
Compound 41: To a stirred solution of 40 (180 mg, 0.267 mmol) in anhydrous DMF (5 mL) was added pyridinium dichromate (603 mg, 1.60 mmol). The reaction mixture was stirred for 48 hours. After dilution with water (20 mL), the mixture was extracted with Et_2O (3x40 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel column chromatography to afford compound 41 (53 mg, 0.075 mmol, 28%, R_f =0.25 developed with CH_2Cl_2 :MeOH:AcOH=95:4.5:0.5). Molecular weight for $\text{C}_{43}\text{H}_{77}\text{O}_5\text{Si}$ (M-H) $^-$ Calc. 701.5540, Found 701.5. This compound can be synthesized by TEMPO oxidation.

Compound 42: A procedure analogous to that described for compound 19 afforded compound 42 (23 mg 0.032 mmol, 21% from compound 40). ^1H NMR (400 MHz, CDCl_3) δ 3.67 (s, 6H), 3.59-3.62 (m, 1H), 2.30 (t, J =7.5 Hz, 4H), 2.13 (t, J =6.8 Hz, 8H), 1.27-1.64 (m, 48H), 0.88 (s, 9H), 0.03 (s, 6H).

Reduction using P-2 nickel conditions can give compound 43 and subsequent deprotection by TBAF can afford compound 8.

Example 5: Alternate Synthesis for Compound 8

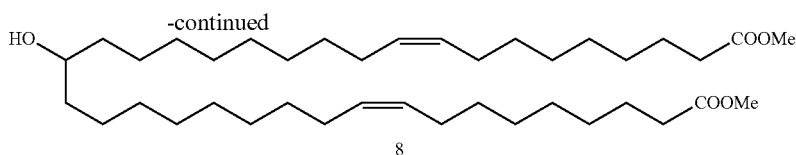
Scheme 5



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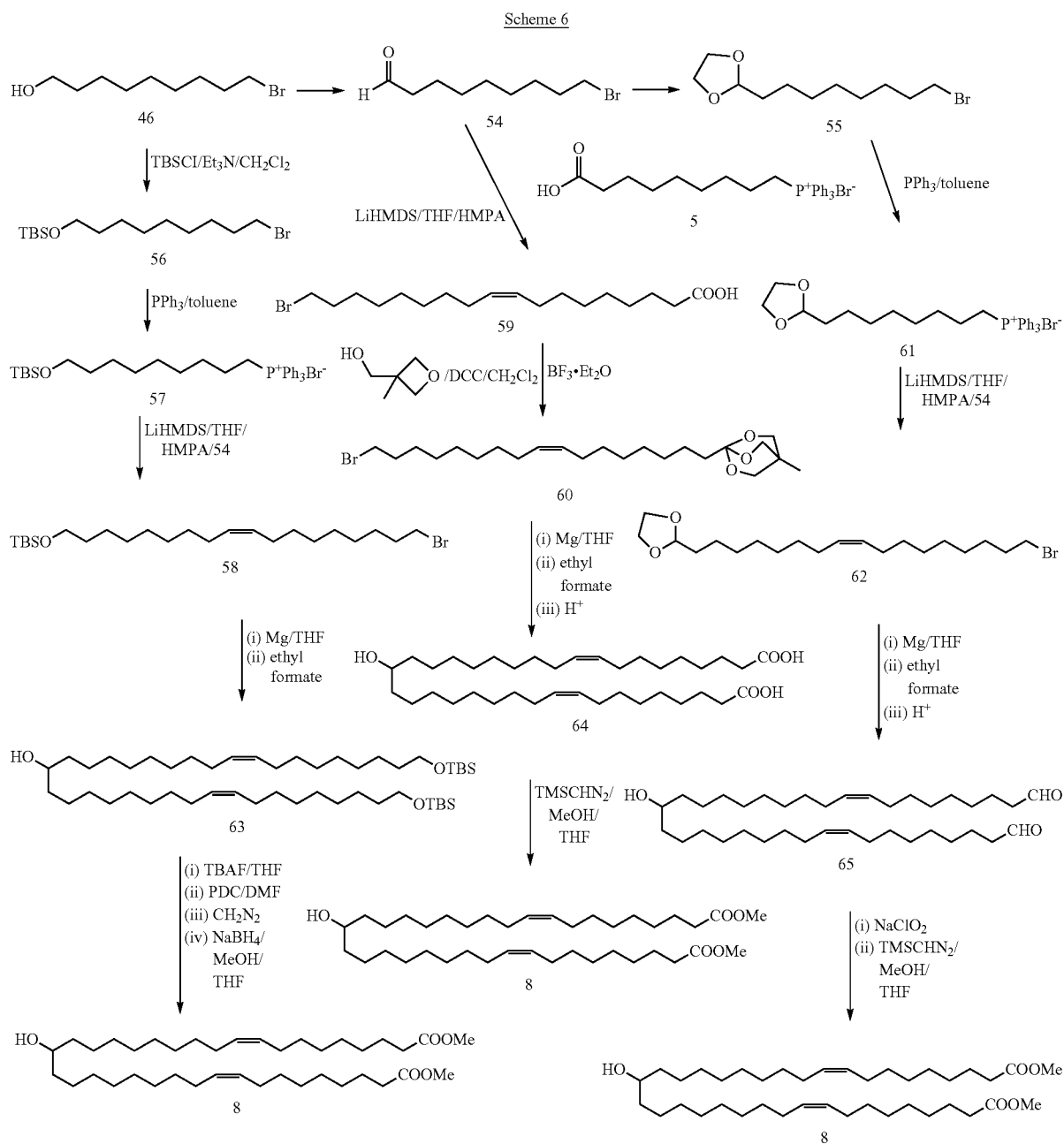
429

430



Compound 8 can be synthesized as shown in Scheme 5. The bromide 51 can be converted to its Grignard reagent¹⁰ then coupled with ethyl formate to afford compound 52. Subsequent acid treatment, oxidation, and reduction can give compound 8.

Example 6: Alternate Synthesis for Compound 8

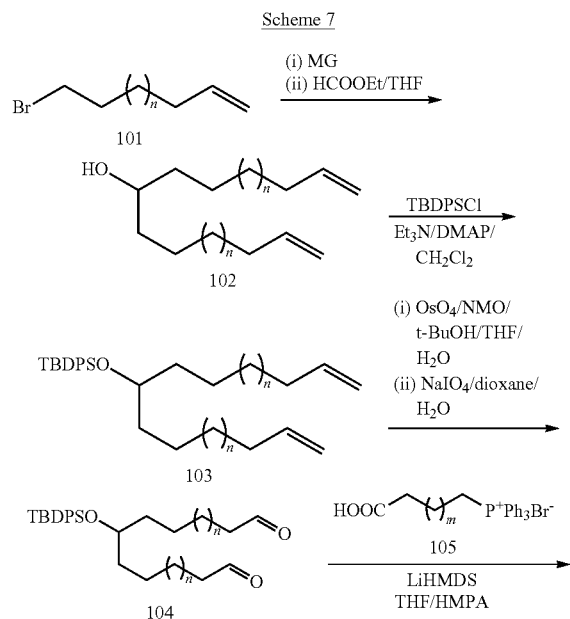


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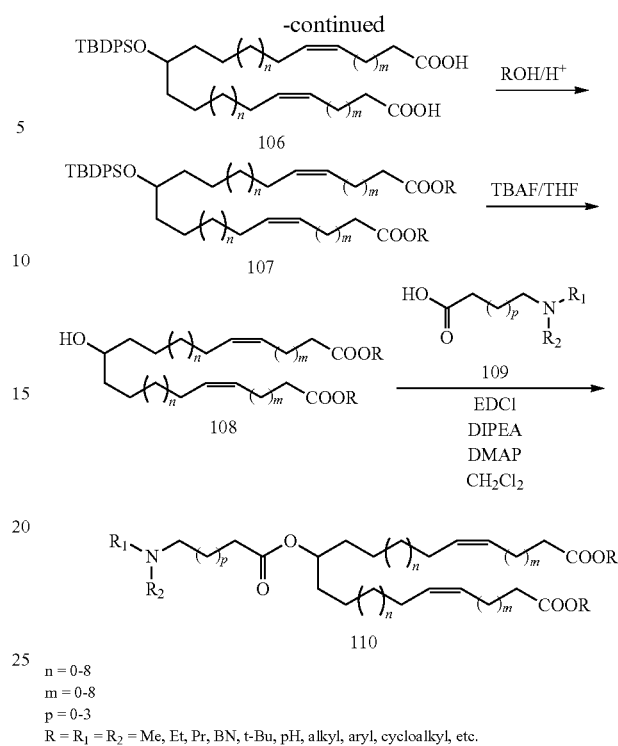
431

Compound 8 can be synthesized as shown in Scheme 6. Either bromides of compound 58, 60, or 62 can be reacted with ethyl formate to generate terminal-functionalized diolefin chain. Compound 8 can then be prepared from the diolefin chain compounds using standard chemical reactions.

Example 7: General Synthetic Scheme for Terminal Ester Lipids

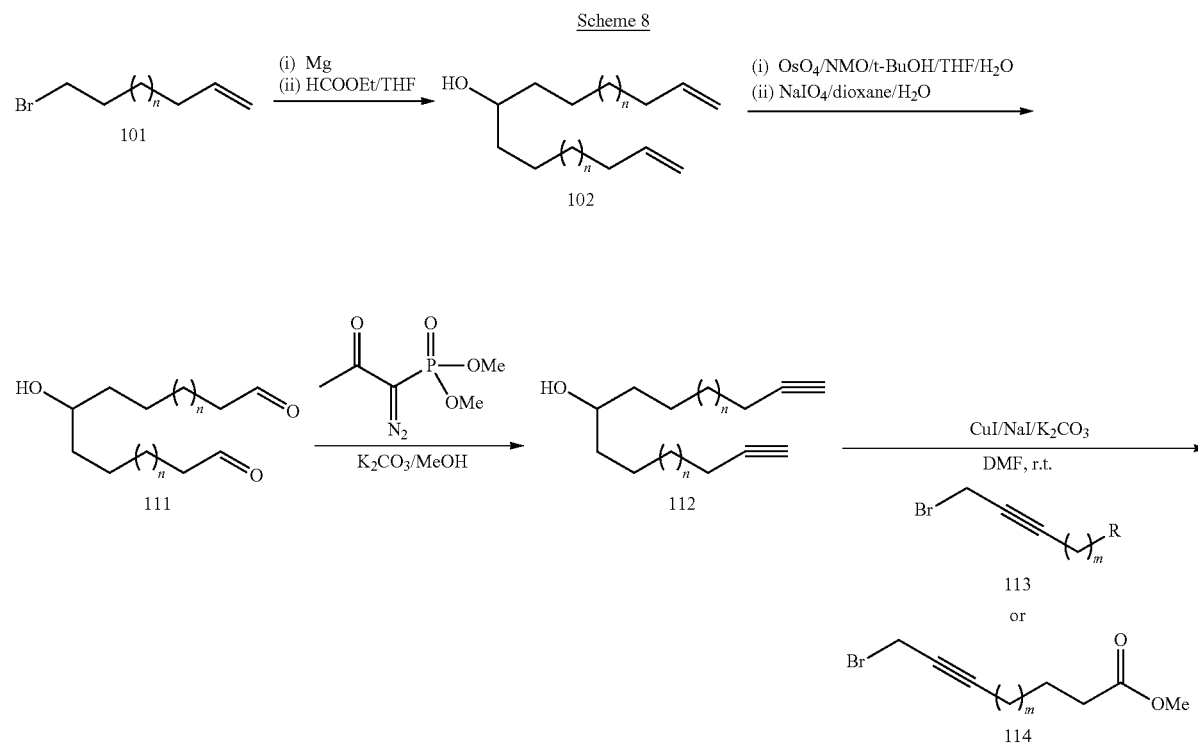


432

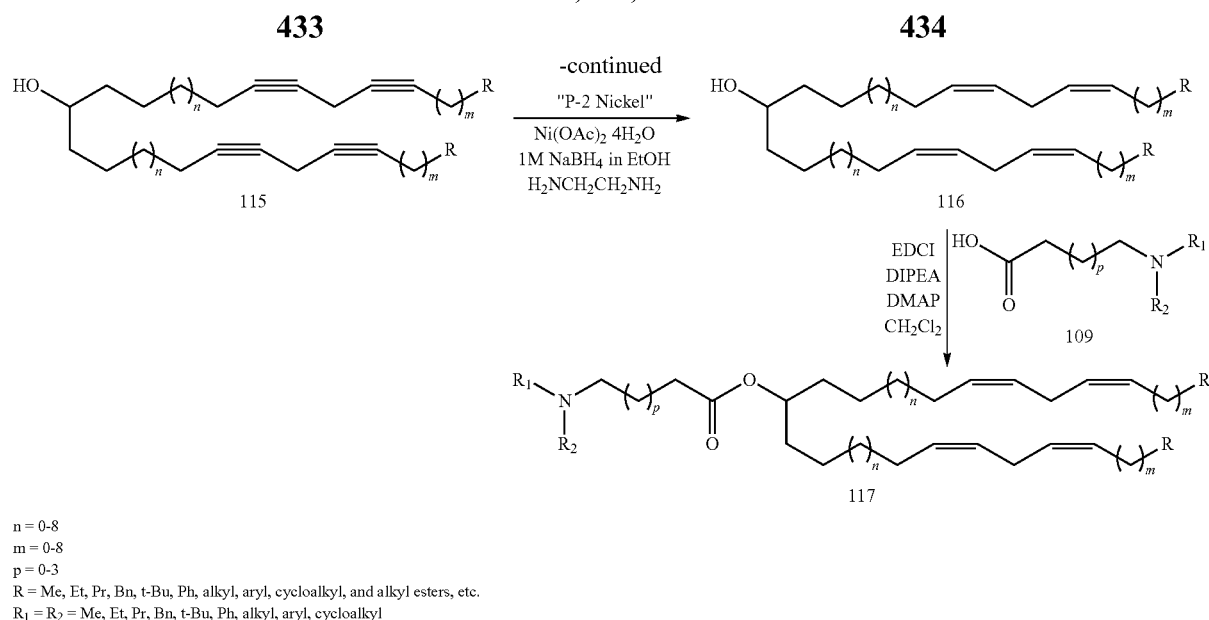


As shown in Scheme 7, chain length and linker length as well as alkyl groups in ester functionality and substituents on nitrogen atom can be derivatized.

Example 8: General Synthetic Scheme 2 for Terminal Ester Lipids



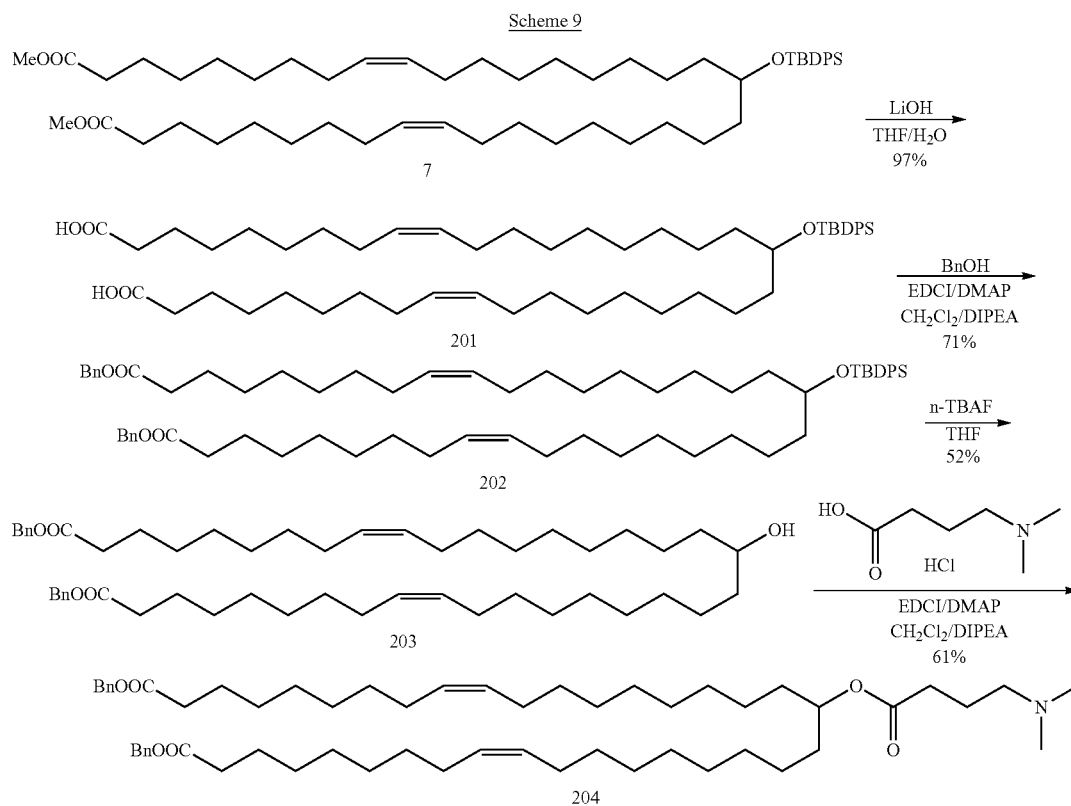
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As shown in Scheme 8, copper-mediated coupling affords di-yne containing lipid chain with terminal functional groups, which can be easily reduced to generate di-ene containing lipid chains. The length of linker and lipid chain as well as functional substituent groups (R , R_1 , R_2) can be derivatized.

Example 9: Synthesis of Terminal Benzyl Ester Lipid

Compound 201: Compound 7 (1.30 g, 1.51 mmol) was treated with lithium hydroxide monohydrate (317 mg, 7.55 mmol) in THF (25 mL) and H_2O (5 mL) for 12 h. Amberlite IR-120 (plus) ion exchange resin was added then stirred for 10 minutes. The resulting clear solution was filtered, washed with THF/ H_2O and evaporated. Co-evaporation with toluene gave the compound 201 (1.22 g, 1.47 mmol, 97%). Molecular weight for $\text{C}_{53}\text{H}_{85}\text{O}_5\text{Si}$ ($M-H$)⁻ Calc. 829.6166, Found 829.5.



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Compound 202: A procedure analogous to that described for compound 9 was followed with benzylalcohol and 201 (101 mg, 0.121 mmol) to afford compound 202 (87 mg, 0.0860 mmol, 71%). ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.66 (m, 4H), 7.42-7.30 (m, 16H), 5.38-5.30 (m, 4H), 5.11 (s, 4H), 3.71-3.68 (m, 1H), 2.35 (t, $J=7.6$ Hz, 4H), 2.04-1.97 (m, 8H), 1.66-1.62 (m, 4H), 1.40-1.07 (m, 44H), 1.04 (s, 9H).

Compound 203: A procedure analogous to that described for compound 8 was followed with 202 (342 mg, 0.338 mmol) to afford compound 203 (136 mg, 0.176 mmol, 52%). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.30 (m, 10H), 5.38-5.30 (m, 4H), 5.11 (s, 4H), 3.57 (brs, 1H), 2.35 (t, $J=7.6$ Hz, 4H), 2.01-1.98 (m, 8H), 1.66-1.60 (m, 4H), 1.45-1.25 (m, 44H).

Compound 204: A procedure analogous to that described for compound 9 was followed with 203 (133 mg, 0.172 mmol) to afford compound 204 (93 mg, 0.105 mmol, 61%). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.26 (m, 10H), 5.38-5.30 (m, 4H), 5.11 (s, 4H), 4.88-4.83 (m, 1H), 2.37-2.27 (m, 8H), 2.22 (s, 6H), 2.03-1.97 (m, 8H), 1.81-1.26 (m, 50H).

Example 10: Synthesis of Terminal t-Butyl Ester Lipid and the Derivatives

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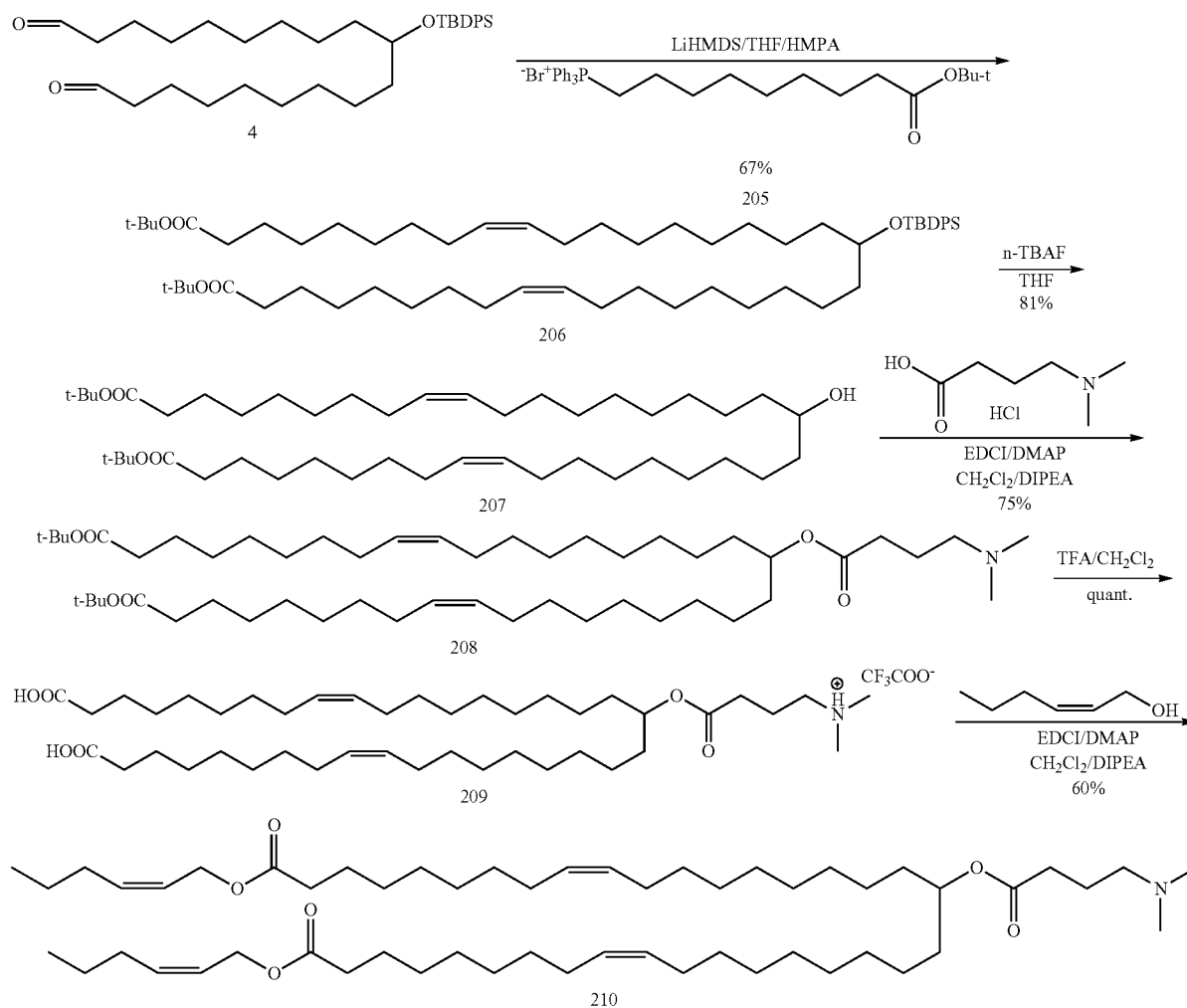
Compound 206: A procedure analogous to that described for compound 12 was followed with 205 (3.80 g, 0.761 mmol) and 4 (1.75 g, 3.17 mmol) to afford compound 206 (2.00 g, 2.12 mmol, 67%). ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.66 (m, 4H), 7.42-7.33 (m, 6H), 5.39-5.31 (m, 4H), 3.71-3.68 (m, 1H), 2.20 (t, $J=7.6$ Hz, 4H), 2.01-1.98 (m, 8H), 1.59-1.55 (m, 4H), 1.44 (s, 18H), 1.41-1.11 (m, 44H), 1.04 (s, 9H).

Compound 207: A procedure analogous to that described for compound 8 was followed with 206 (265 mg, 0.281 mmol) to afford compound 207 (161 mg, 0.228 mmol, 81%). ^1H NMR (400 MHz, CDCl_3) δ 5.38-5.30 (m, 4H), 3.58 (brs, 1H), 2.20 (t, $J=7.4$ Hz, 4H), 2.01-1.98 (m, 8H), 1.59-1.55 (m, 4H), 1.44 (s, 18H), 1.35-1.26 (m, 44H).

Compound 208: A procedure analogous to that described for compound 9 was followed with 207 (158 mg, 0.224 mmol) to afford compound 208 (138 mg, 0.169 mmol, 75%). Molecular weight for $\text{C}_{51}\text{H}_{96}\text{NO}_6$ ($\text{M}+\text{H}$) $^+$ Calc. 818.7238, Found 818.7.

Compound 209: Compound 208 (148 mg, 0.181 mmol) was treated with TFA (1.5 mL) in CH_2Cl_2 (6 mL) for 2.5 h. After evaporation and co-evaporation with toluene gave the compound 209 (154 mg, quant.). Molecular weight for $\text{C}_{43}\text{H}_{80}\text{NO}_6$ ($\text{M}+\text{H}$) $^+$ Calc. 706.5980, Found 706.5.

Scheme 10



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Compound 210: A procedure analogous to that described for compound 9 was followed with 209 (0.061 mmol) and *cis*-2-Hexen-1-ol (18.3 mg, 0.183 mmol) to afford compound 210 (32 mg, 0.0368 mmol, 60%). Molecular weight for $C_{55}H_{100}NO_6$ (M+H)⁺ Calc. 870.7551, Found 870.5.

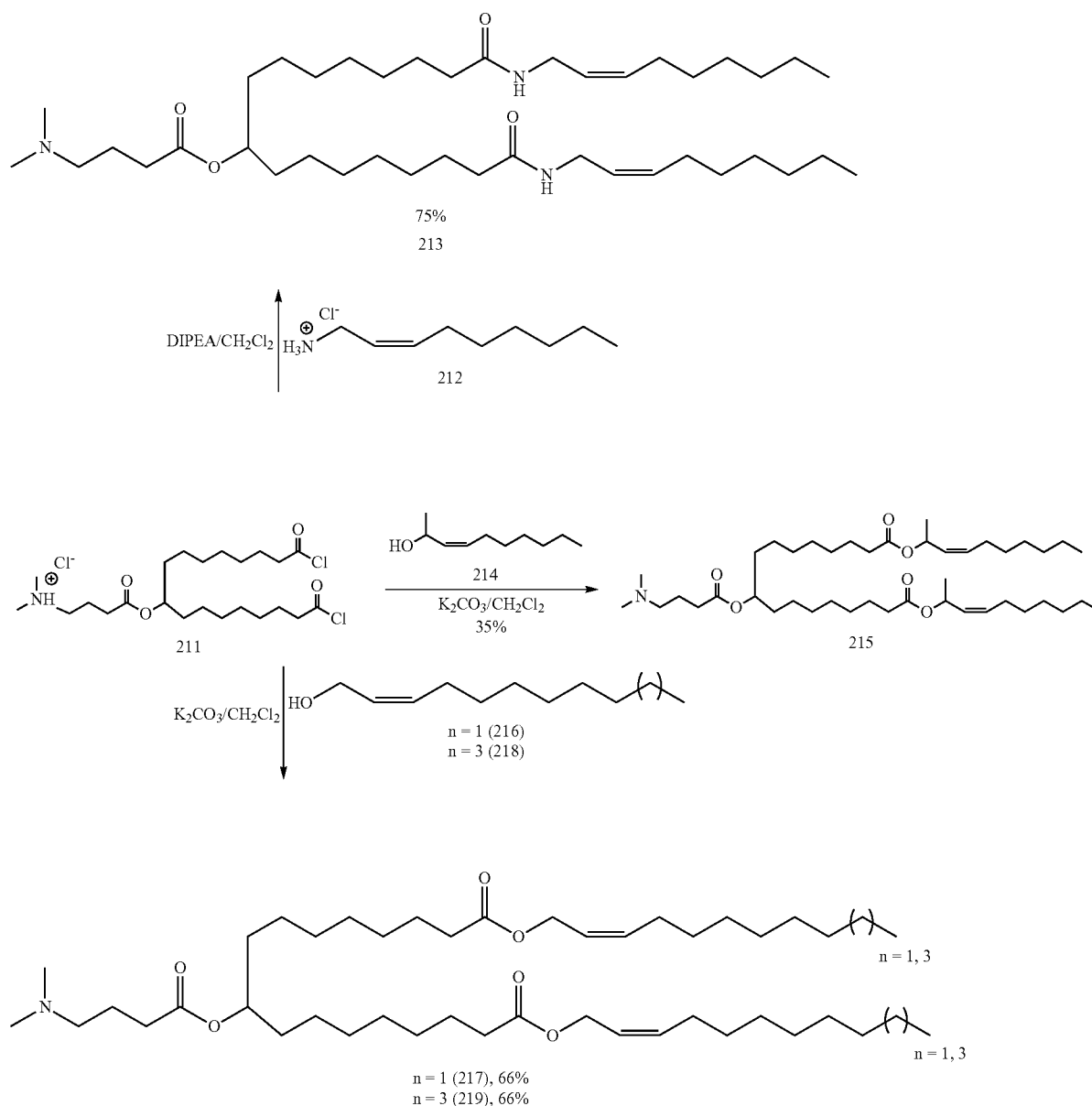
Example 11: Synthesis of Internal Ester/Amide
Lipids-1

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mmol) in CH_2Cl_2 (35 mL) for 14 h. Aqueous work-up then column chromatography gave compound 215 (244 mg, 0.346 mmol, 35%). Molecular weight for $C_{43}H_{80}NO_6$ (M+H)⁺ Calc. 706.5986, Found 706.4.

Compound 217: Compound 211 (425 mg, 0.845 mmol) was treated with 216 (525 mg, 3.08 mmol) and K_2CO_3 (1.17 g, 8.45 mmol) in CH_2Cl_2 (35 mL) for 14 h. Aqueous work-up then column chromatography gave compound 217

Scheme 11



Compound 213: Compound 211 (503 mg, 1.0 mmol) was treated with 212 (533 mg, 3.0 mmol) in CH_2Cl_2 (35 mL) and DIPEA (1.74 mL, 10 mmol) for 14 h. Aqueous work-up then column chromatography gave compound 213 (506 mg, 0.748 mmol, 75%). Molecular weight for $C_{41}H_{78}N_3O_4$ (M+H)⁺ Calc. 676.5992, Found 676.4.

Compound 215: Compound 211 (503 mg, 1.0 mmol) was treated with 214 (469 mg, 3.0 mmol) and K_2CO_3 (1.38 g, 10

(407 mg, 0.554 mmol, 66%). Molecular weight for $C_{45}H_{84}NO_6$ (M+H)⁺ Calc. 734.6299, Found 734.4.

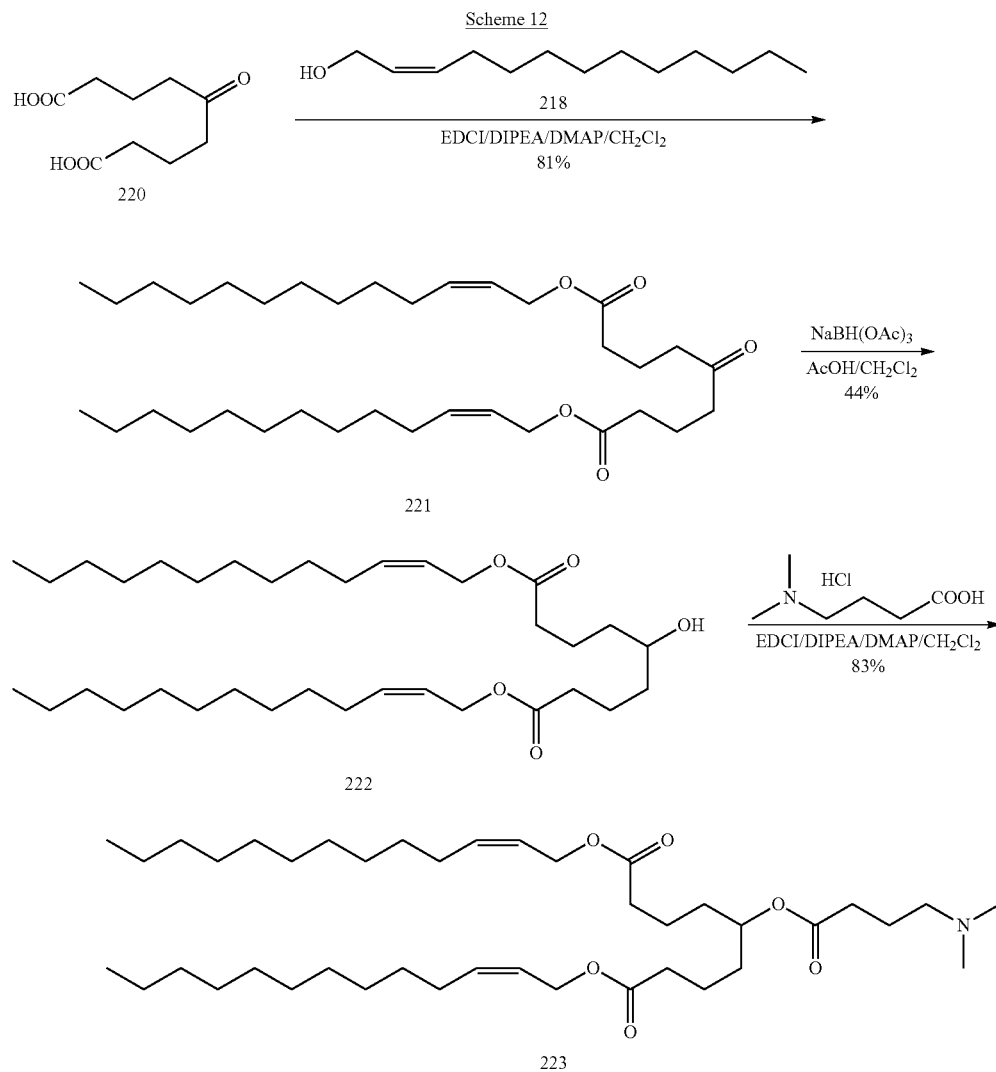
Compound 219: Compound 211 (503 mg, 1.0 mmol) was treated with 218 (595 mg, 3.0 mmol) and K_2CO_3 (1.38 g, 10 mmol) in CH_2Cl_2 (35 mL) for 14 h. Aqueous work-up then column chromatography gave compound 219 (519 mg, 0.657 mmol, 66%). Molecular weight for $C_{49}H_{92}NO_6$ (M+H)⁺ Calc. 790.6925, Found 790.7.

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Example 12: Synthesis of Internal Ester Lipid-223



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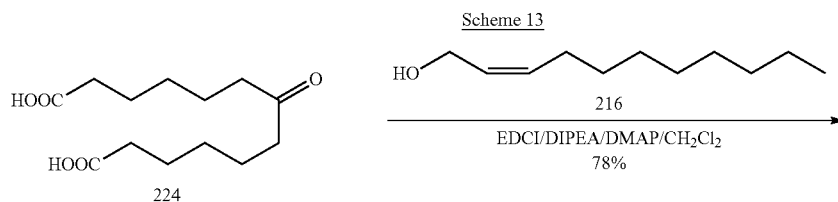
Compound 221: A procedure analogous to that described for compound 9 was followed with 220 (390 mg, 1.93 mmol) and 218 (765 mg, 3.86 mmol) to afford compound 221 (878 mg, 1.56 mmol, 81%). ¹H NMR (400 MHz, CDCl₃) δ 5.67-5.61 (m, 2H), 5.54-5.48 (m, 2H), 4.62 (d, J=6.8 Hz, 4H), 2.47 (t, J=7.2 Hz, 4H), 2.33 (t, J=7.2 Hz, 4H), 2.12-2.06 (m, 4H), 1.93-1.86 (m, 4H), 1.38-1.26 (m, 32H), 0.88 (t, J=6.8 Hz, 6H).

Compound 222: Compound 221 (318 mg, 0.565 mmol) was treated with NaBH(OAc)₃ (360 mg, 1.70 mmol) in CH₂Cl₂ (5 mL) and AcOH (0.2 mL) for 16 h. After evapo-

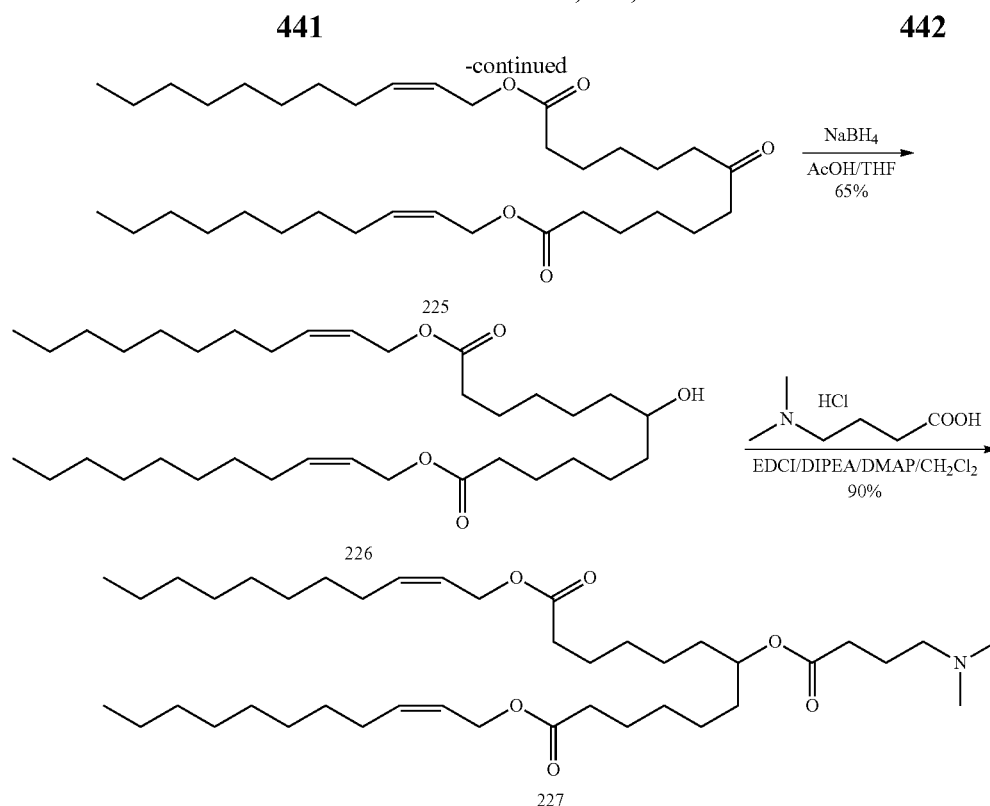
ration, column chromatography gave compound 222 (141 mg, 0.250 mmol, 44%). Molecular weight for C₃₅H₆₅O₅ (M+H)⁺ Calc. 565.4832, Found 565.4.

Compound 223: A procedure analogous to that described for compound 9 was followed with 222 (137 mg, 0.243 mmol) to afford compound 223 (137 mg, 0.202 mmol, 83%). Molecular weight for C₄₁H₇₆NO₆ (M+H)⁺ Calc. 678.5673, Found 678.5.

Example 13: Synthesis of Internal Ester Lipid-227



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Compound 225: A procedure analogous to that described for compound 9 was followed with 224 (200 mg, 0.774 mmol) and 216 (264 mg, 1.55 mmol) to afford compound 225 (341 mg, 0.606 mmol, 78%). Molecular weight for $C_{35}H_{62}NaO_5$ (M+Na)⁺ Calc. 585.4495, Found 585.5.

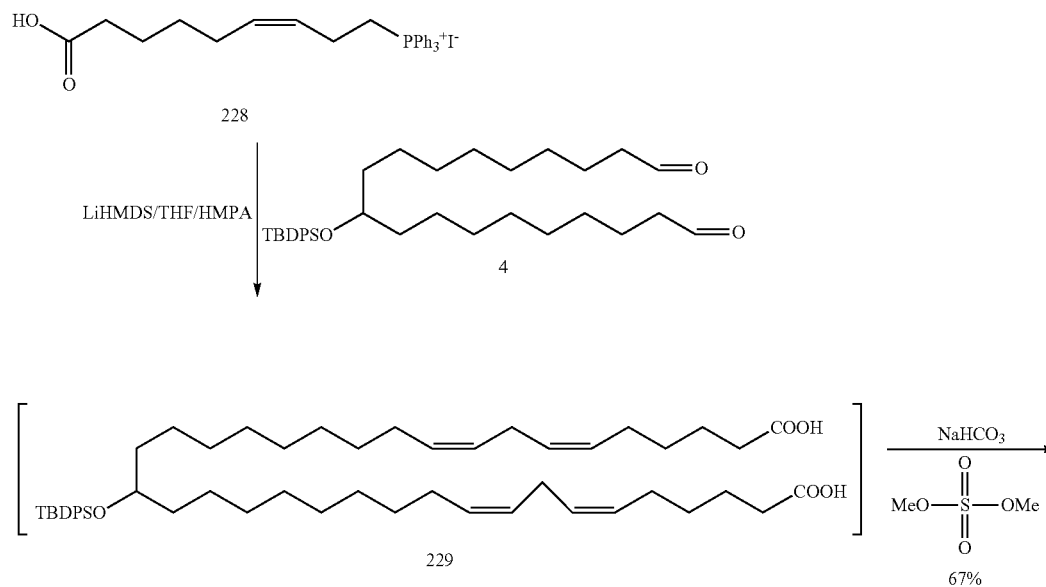
Compound 226: Compound 225 (283 mg, 0.503 mmol) was treated with $NaBH_4$ (57 mg, 1.51 mmol) in THF (5 mL) and AcOH (0.2 mL) for 8 h. After evaporation, column chromatography gave compound 226 (185 mg, 0.328 mmol,

65%). Molecular weight for $C_{35}H_{64}NaO_5$ (M+Na)⁺ Calc. 587.4651, Found 587.3.

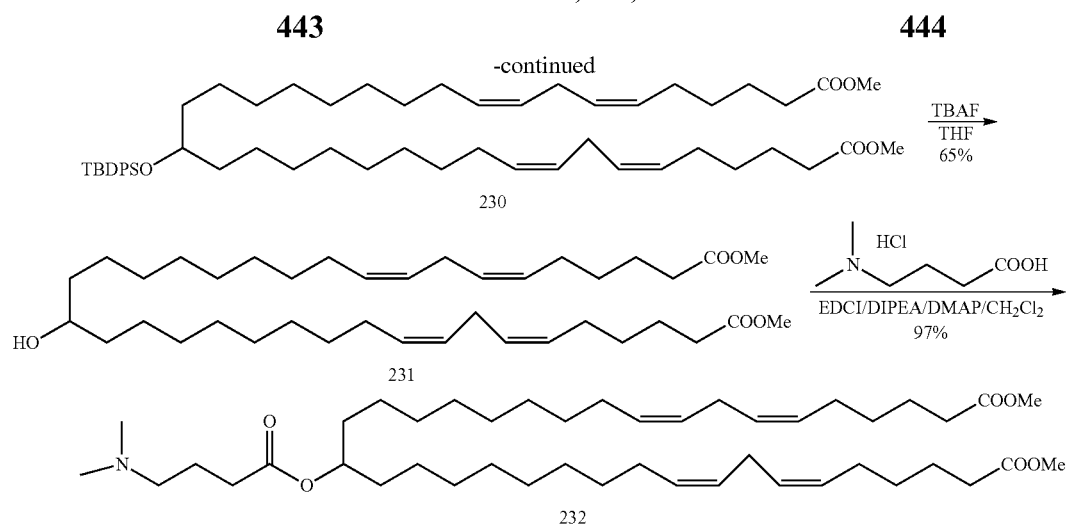
Compound 227: A procedure analogous to that described for compound 9 was followed with 226 (230 mg, 0.407 mmol) to afford compound 227 (248 mg, 0.366 mmol, 90%). Molecular weight for $C_{41}H_{76}NO_6$ (M+H)⁺ Calc. 678.5673, Found 678.5.

Example 14: Synthesis of Terminal Ester Lipid with Linoleyl Chain-232

Scheme 14



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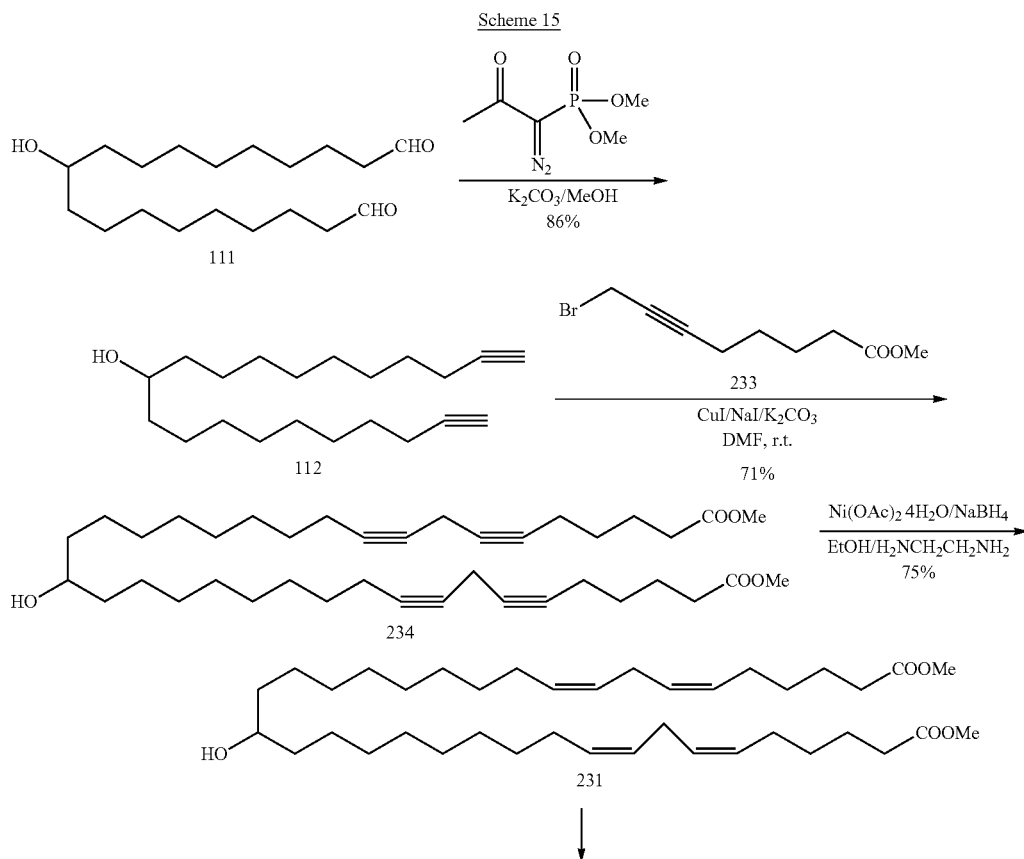
Compound 230: A procedure analogous to that described for compound 7 was followed with 228 (3.27 g, 6.0 mmol) and 4 (1.27 g, 2.30 mmol) to afford compound 230 (1.31 g, 1.53 mmol, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.66 (m, 4H), 7.42-7.33 (m, 6H), 5.42-5.29 (m, 8H), 3.71-3.68 (m, 1H), 3.66 (s, 6H), 2.77 (t, J=5.8 Hz, 4H), 2.33-2.28 (m, 4H), 2.11-2.01 (m, 8H), 1.69-1.60 (m, 4H), 1.43-1.10 (m, 32H), 1.04 (s, 9H).

Compound 231: A procedure analogous to that described for compound 8 was followed with 230 (1.30 g, 1.52 mmol) to afford compound 231 (611 mg, 0.990 mmol, 65%). ¹H

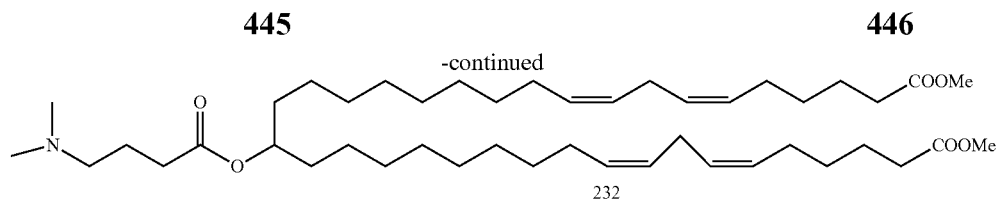
NMR (400 MHz, CDCl₃) δ 5.41-5.29 (m, 8H), 3.67 (s, 6H), 3.58 (brs, 1H), 2.77 (t, J=5.8 Hz, 4H), 2.32 (t, J=7.4 Hz, 4H), 2.10-2.00 (m, 8H), 1.69-1.60 (m, 4H), 1.43-1.29 (m, 32H).

Compound 232: A procedure analogous to that described for compound 9 was followed with 231 (520 mg, 0.843 mmol) to afford compound 232 (600 mg, 0.822 mmol, 97%). Molecular weight for C₄₅H₈₀NO₆ (M+H)⁺ Calc. 730.5986, Found 730.5.

Example 15: Synthesis of Terminal Ester Lipid with Linoleyl Chain-232



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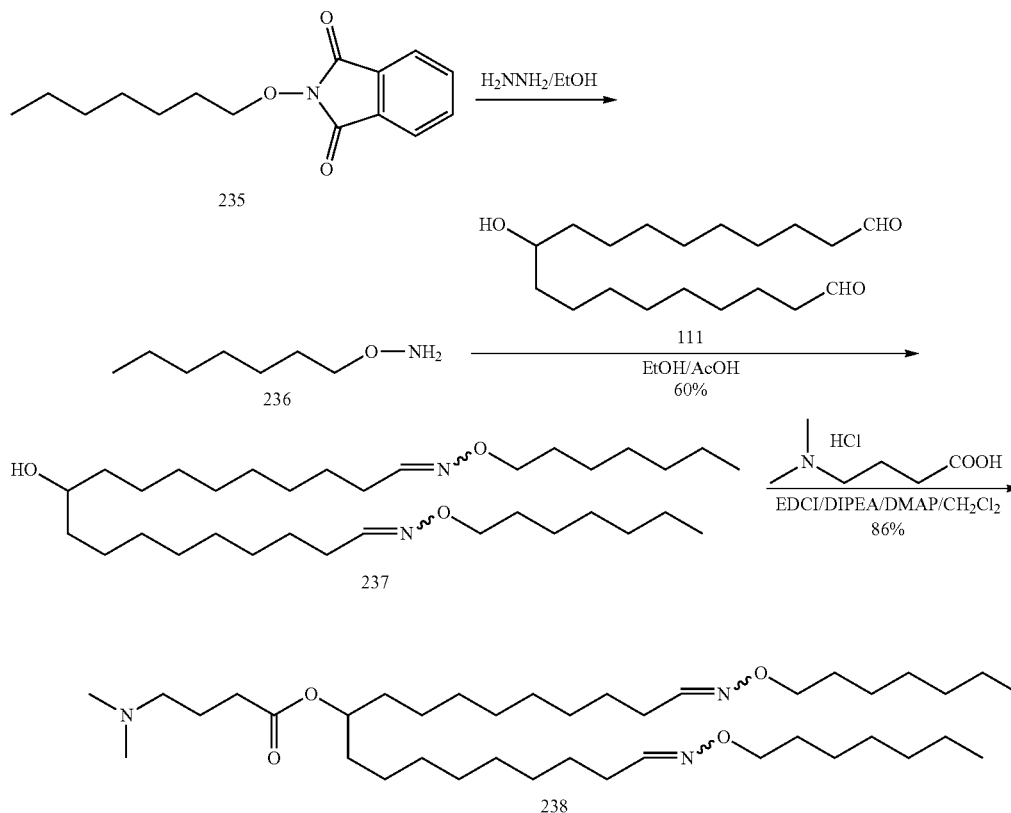
Compound 231 was also synthesized as shown Scheme 15.

Compound 112: Compound 111 (840 mg, 2.69 mmol) was treated with dimethyl (1-diazo-2-oxopropyl)phosphonate (0.970 mL, 6.46 mmol) and K_2CO_3 (1.49 g, 10.8 mmol) in MeOH (40 mL) for 6 h. Aqueous work-up then column chromatography gave compound 112 (700 mg, 2.30 mmol,

mmol) and a solution of 234 (290 mg, 0.476 mmol) in EtOH (3 mL) was added then stirred for 1 h. The reaction mixture was filtered through Celite and evaporated. Aqueous work-up then column chromatography gave compound 231 (219 mg, 0.355 mmol, 75%). Molecular weight for $C_{39}H_{69}O_5$ (M+H)⁺ Calc. 617.5145, Found 617.3.

Example 16: Synthesis of Internal Oxime Lipid-238

Scheme 16



86%). ¹H NMR (400 MHz, CDCl₃) δ 3.58 (brs, 1H), 2.18 (td, J=7.1, 2.6 Hz, 4H), 1.94 (t, J=2.6 Hz, 2H), 1.56-1.25 (m, 28H).

Compound 234: Compound 112 (207 mg, 0.680 mmol) was treated with 233 (316 mg, 1.36 mmol), K_2CO_3 (282 mg, 2.04 mmol), NaI (408 mg, 2.72 mmol) and CuI (518 mg, 2.72 mmol) in DMF (3.5 mL) for 18 h. Aqueous work-up then column chromatography gave compound 234 (292 mg, 0.480 mmol, 71%). Molecular weight for $C_{39}H_{61}O_5$ (M+H)⁺ Calc. 609.4519, Found 609.5.

Compound 231: To a stirred solution of nickel(II) acetate tetrahydrate (533 mg, 2.14 mmol) in EtOH (28.5 mL), 1 M solution of NaBH₄ in EtOH (2.14 mL) was added at room temperature. After 30 min, ethylenediamine (0.574 mL, 8.57

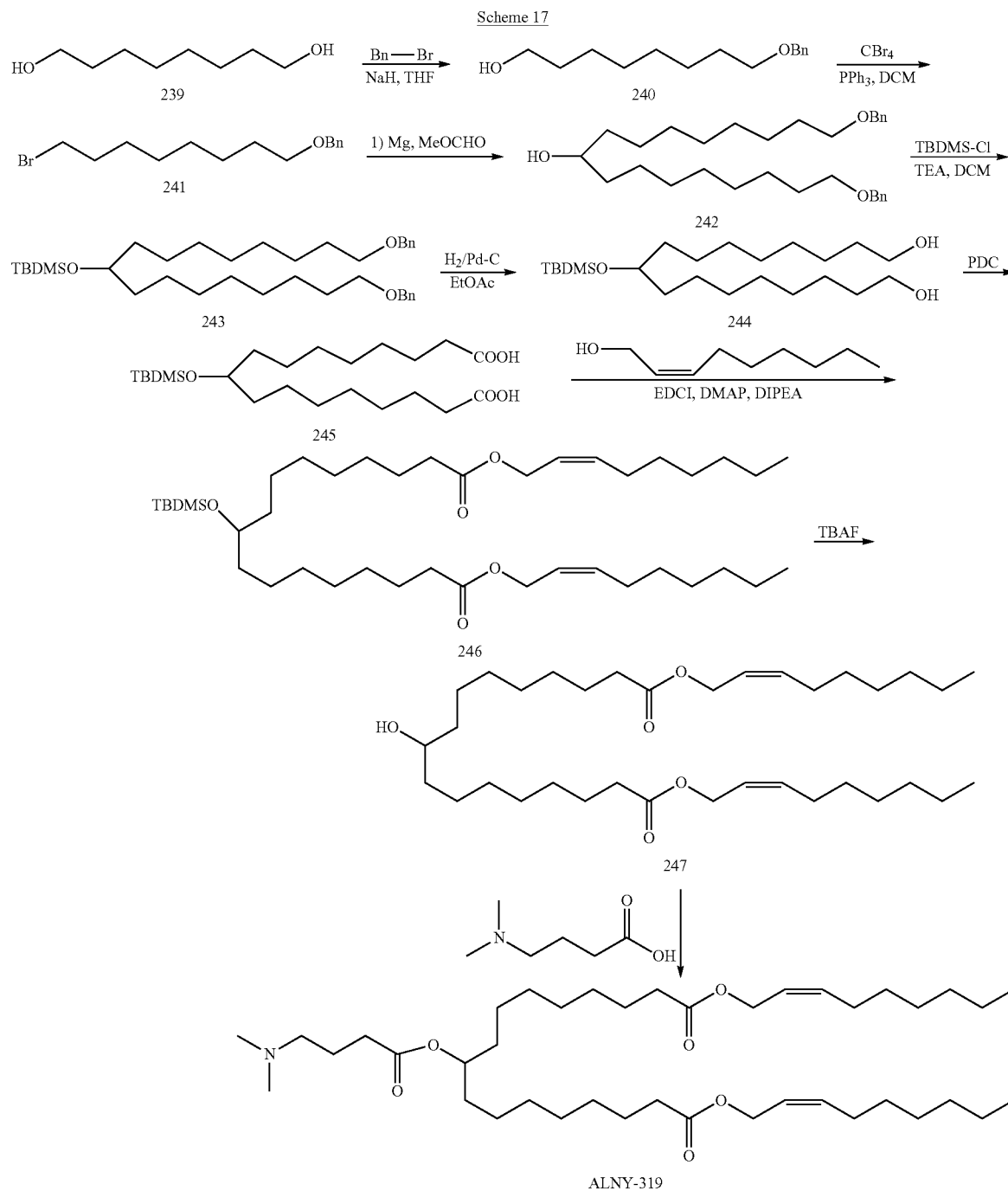
Compound 237: Compound 235 (465 mg, 1.78 mmol) was treated with hydrazine monohydrate (64-65%, 0.135 mL, 1.78 mmol) in EtOH (15 mL) for 4 h. After filtration then evaporation, the crude was re-suspended in EtOH (5 mL). To this solution was added compound 111 (160 mg, 0.512 mmol) and AcOH (a few drops). Aqueous work-up then column chromatography gave compound 237 (165 mg, 0.306 mmol, 60%). Molecular weight for $C_{33}H_{67}N_2O_3$ (M+H)⁺ Calc. 539.5152, Found 539.3.

Compound 238: A procedure analogous to that described for compound 9 was followed with 237 (162 mg, 0.301 mmol) to afford compound 238 (168 mg, 0.258 mmol, 86%). Molecular weight for $C_{39}H_{78}N_3O_4$ (M+H)⁺ Calc. 652.5992, Found 652.4.

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Example 17

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8-benzyloxy-octan-1-ol (240): To a stirred suspension of NaH (60% in oil, 82 g, 1.7096 mol) in 500 mL anhydrous DMF, a solution of compound 239 (250 g, 1.7096 mol) in 1.5 L DMF was added slowly using a dropping funnel at 0° C. The reaction mixture was stirred for 30 minutes, then benzyl bromide (208.86 mL, 1.7096 mol) was added slowly under a nitrogen atmosphere. The reaction was then warmed to ambient temperature and stirred for 10 hours. After completion of reaction, the mixture was quenched with crushed ice (~2 kg) and extracted with ethyl acetate (2x1 L).

The organic layer washed with water (1 L) to remove unwanted DMF, dried over Na₂SO₄ and evaporated to dryness under vacuum. The crude compound was purified on 60-120 silica gel, eluted with 0-5% MeOH in DCM to afford compound 240 (220 g, 54%) as pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 5H), 4.49 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 1.63-1.51 (m, 4H), 1.39-1.23 (m, 8H).

(8-bromo-octyloxymethyl)-benzene (241): Compound 240 (133 g, 0.5635 mol) was dissolved in 1.5 L of DCM,

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CBr₄ (280.35 g, 0.8456 mol) was added to this stirring solution and the reaction mixture was cooled to 0° C. under an inert atmosphere. PPh₃ (251.03 g, 0.9571 mol) was then added in portions maintaining the temperature below 20° C. and after complete addition, the reaction mixture was stirred for 3 hours at room temperature. After completion of reaction, solid (PPh₃O) precipitated out from the reaction mixture was isolated by filtration and the filtrate was diluted with crushed ice (~1.5 kg) and extracted with DCM (3×750 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and distilled under vacuum. The resulting crude compound was chromatographed on 60-120 mesh silica gel column using 0-5% ethyl acetate in hexanes as eluting system to afford compound 241 (150 g, 89%) as pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.47-3.41 (m, 2H), 3.41-3.37 (m, 2H), 1.86-1.80 (m, 4H), 1.62-1.56 (m, 2H), 1.42-1.29 (m, 8H).

1, 17-bis-benzyloxy-heptadecan-9-ol (242): To freshly activated Mg turnings (24.08 g, 1.003 mol) was added 200 mL anhydrous THF, followed by the addition of pinch of iodine into the mixture under inert atmosphere. After initiation of the Grignard formation a solution of Compound 241 (150 g, 0.5016 mol) in 1 L of dry THF was added slowly controlling the exothermic reaction. After complete addition, the reaction was heated to reflux for 1 hour, then cooled to room temperature. Methyl formate (60.24 g, 1.0033 mol) was then added slowly and reaction was continued for 2 hours. After completion, the reaction was quenched by slow addition of 10% HCl followed by water (1 L) and extracted with ethyl acetate (3×1 L). The organic layer was taken in 5 litre beaker, diluted with 500 mL of methanol and cooled to 0° C. To this solution excess of NaBH₄ (~5 eq) was added in portions to ensure the hydrolysis of formate ester which was not cleaved by addition of HCl. The resulting solution was stirred for an hour and then volatiles were removed under vacuum. The residue was taken in water (1 L) and acidified by 10% HCl solution (pH 4). The product was then extracted with ethyl acetate (3×1 L). The organic phase was then dried and concentrated on rotary evaporator to afford compound 242 (57 g, 24%) as solid. ¹H NMR (400 MHz, CDCl₃): δ=7.35-7.32 (m, 8H), 7.29-7.24 (m, 2H), 4.49 (s, 4H), 3.56 (m, 1H), 3.46-3.43 (m, 4H), 1.63-1.56 (m, 4H), 1.44-1.34 (m, 28H). ¹³C NMR (100 MHz, CDCl₃): δ=138.56, 128.21, 127.49, 127.34, 72.72, 71.76, 70.37, 37.37, 29.64, 29.56, 29.47, 29.33, 26.07, 25.54.

[9-benzyloxy-1-(8-benzyloxy-octyl)-nonyloxy]-tert-butyl-dimethyl-silane (243): Compound 242 (56 g, 0.1196 mol) was dissolved in 700 mL of anhydrous THF and cooled to 0° C. TBMS-Cl (36.06 g, 0.2396 mol) was added slowly followed by addition of imidazole (32.55 g, 0.4786 mol) under an inert atmosphere. The reaction was then stirred at room temperature for 18 hours, then quenched with ice (~1 kg). The product was extracted with ethyl acetate (3×500 mL). The organic layer was separated, washed with saturated NaHCO₃ solution to remove the acidic impurity, dried over Na₂SO₄ and evaporated under reduce pressure to obtain crude compound which was purified by silica gel (60-120 mesh) and eluted with 0-10% ethyl acetate hexane to afford (60 g, 82%) of compound 243 as yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 10H), 4.49 (s, 4H), 3.60-3.57 (m, 1H), 3.46-3.43 (m, 4H), 1.61-1.54 (m, 4H), 1.41-1.26 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H) 9-(tert-butyl-dimethyl-silanyloxy)-heptadecane-1, 17-diol (244): Compound 243 (60 g, 0.1030 mol) was dissolved in 500 mL ethyl acetate and degassed with N₂ for 20 min. (10 wt %) Pd on carbon (12 g) was added and reaction was stirred under an atmosphere of hydrogen for 18 hours. After completion, the

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mixture was filtered through a bed of celite and washed with ethyl acetate. The filtrate was evaporated under vacuum. Compound 244 (19 g, 46%) thus obtained was pure enough to carry out the next reaction. ¹H NMR (400 MHz, CDCl₃): δ=3.64-3.58 (m, 5H), 1.59 (br, 2H), 1.57-1.51 (m, 4H), 1.38-1.22 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H).

9-(tert-butyl-dimethyl-silanyloxy)-heptadecanedioic acid (245): To a stirred solution of 244 (2 g, 0.0049 mol) in anhydrous DMF (40 mL) was added pyridinium dichromate (2.7 g, 0.0074 mol) at 0° C. under an inert atmosphere. The reaction mixture was then allowed to warm to room temperature over a period of 10-15 minutes and continued for 24 hours. Then, the reaction was diluted with water (100 mL). The aqueous phase was extracted using DCM (3×40 mL). The organic phase was washed with brine (1×25 mL) and concentrated under vacuum to afford crude acid which was then purified by (100-200 mesh) silica gel column using 0-30% ethyl acetate in hexanes system. Pure product (245) was obtained (0.7 g, 33%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ=3.61-3.56 (m, 1H), 2.35-2.32 (m, 4H), 1.64-1.59 (m, 4H), 1.40-1.19 (m, 24H), 0.86 (s, 9H), 0.017 (s, 6H); LC-MS [M+H]—431.00; HPLC (ELSD) purity ~96.94%

Di((Z)-non-2-en-1-yl) 9-((tert-butyl-dimethylsilyl)oxy)heptadecanedioate (246): The diacid 245 (0.42 g, 0.97 mmol) was dissolved in 20 mL of dichloromethane and to it cis-2-nonen-1-ol (0.35 g, 2.44 mmol) was added followed by Hunig's base (0.68 g, 4.9 mmol) and DMAP (12 mg). To this mixture EDCI (0.47 g, 2.44 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with CH₂Cl₂ (40 mL) and washed with saturated NaHCO₃ (50 mL), water (60 mL) and brine (60 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and solvents were removed in vacuo. The crude product thus obtained was purified by Combiflash Rf purification system (40 g silicagel, 0-10% MeOH in CH₂Cl₂) to afford the pure product 246 (0.35 g, 53%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ ¹H NMR (400 MHz, CDCl₃) δ 5.64 (dt, J=10.9, 7.4 Hz, 2H), 5.58-5.43 (m, 2H), 4.61 (d, J=6.8 Hz, 4H), 3.71-3.48 (m, 1H), 2.30 (t, J=7.6 Hz, 4H), 2.20-1.98 (m, 4H), 1.71-1.53 (m, 4H), 1.31 (ddd, J=8.3, 7.0, 3.7 Hz, 34H), 1.07-0.68 (m, 14H), 0.02 (s, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 178.18, 139.81, 127.78, 81.73, 81.42, 81.10, 76.72, 64.59, 41.52, 41.32, 38.76, 36.09, 34.10, 33.93, 33.80, 33.70, 33.59, 33.55, 33.26, 31.95, 30.34, 29.69, 29.58, 29.39, 27.01, 22.56, 18.48, 0.01.

Di((Z)-non-2-en-1-yl) 9-hydroxyheptadecanedioate (247): The silyl protected diester 246 (0.3 g, 0.44 mmol) was dissolved in 1 M solution of TBAF in THF (6 mL) and the solution was kept at 40° C. for two days. The reaction mixture was diluted with water (60 mL) and extracted with ether (2×50 mL). The combined organic layers were concentrated and the thus obtained crude product was purified by column to isolate the pure product (0.097 g, 39%). ¹H NMR (400 MHz, CDCl₃) δ 5.64 (dt, J=10.9, 7.4 Hz, 2H), 5.52 (dt, J=11.0, 6.8 Hz, 2H), 4.61 (d, J=6.8 Hz, 4H), 3.57 (s, 1H), 2.30 (t, J=7.5 Hz, 4H), 2.09 (q, J=7.1 Hz, 4H), 1.75-1.53 (m, 4H), 1.53-1.06 (m, 36H), 0.88 (t, J=6.8 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 173.98, 135.64, 123.57, 77.54, 77.22, 76.91, 72.14, 60.41, 37.69, 34.54, 31.89, 29.70, 29.60, 29.44, 29.29, 29.07, 27.76, 25.80, 25.15, 22.82, 14.29.

Di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate: The alcohol 247 (0.083 g, 0.147 mmol) was dissolved in 20 mL of dichloromethane and to it dimethylaminobutyric acid hydrochloride (0.030 g, 0.176

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mmol) was added followed by Hunig's base (0.045 g, 0.44 mmol) and DMAP (2 mg). To this mixture EDCI (0.034 g, 0.176 mmol) was added and the reaction mixture was stirred at room temperature overnight and the TLC (silica gel, 10% MeOH in CH₂Cl₂) showed complete disappearance of the starting alcohol. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with saturated NaHCO₃ (50 mL), water (60 mL) and brine (60 mL). The combined organic layers were dried over anhyd. Na₂SO₄ and solvents were removed in vacuo. The crude product thus obtained was purified by Combiflash Rf purification system (40 g silicagel, 0-10% MeOH in CH₂Cl₂) to isolate the pure product (0.062 g, 62%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.74-5.58 (m, 2H), 5.51 (dt, J=9.7, 6.8, 1.3 Hz, 2H), 4.95-4.75 (m, 1H), 4.61 (d, J=6.8 Hz, 4H), 2.35-2.24 (m, 8H), 2.22 (d, J=7.9 Hz, 6H), 2.09 (q, J=6.9 Hz, 4H), 1.83-1.72 (m, 2H), 1.60 (dd, J=14.4, 7.2 Hz, 4H), 1.49 (d, J=5.7 Hz, 4H), 1.41-1.13 (m, 30H), 0.88 (t, J=6.9 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 173.72, 173.36, 135.40,

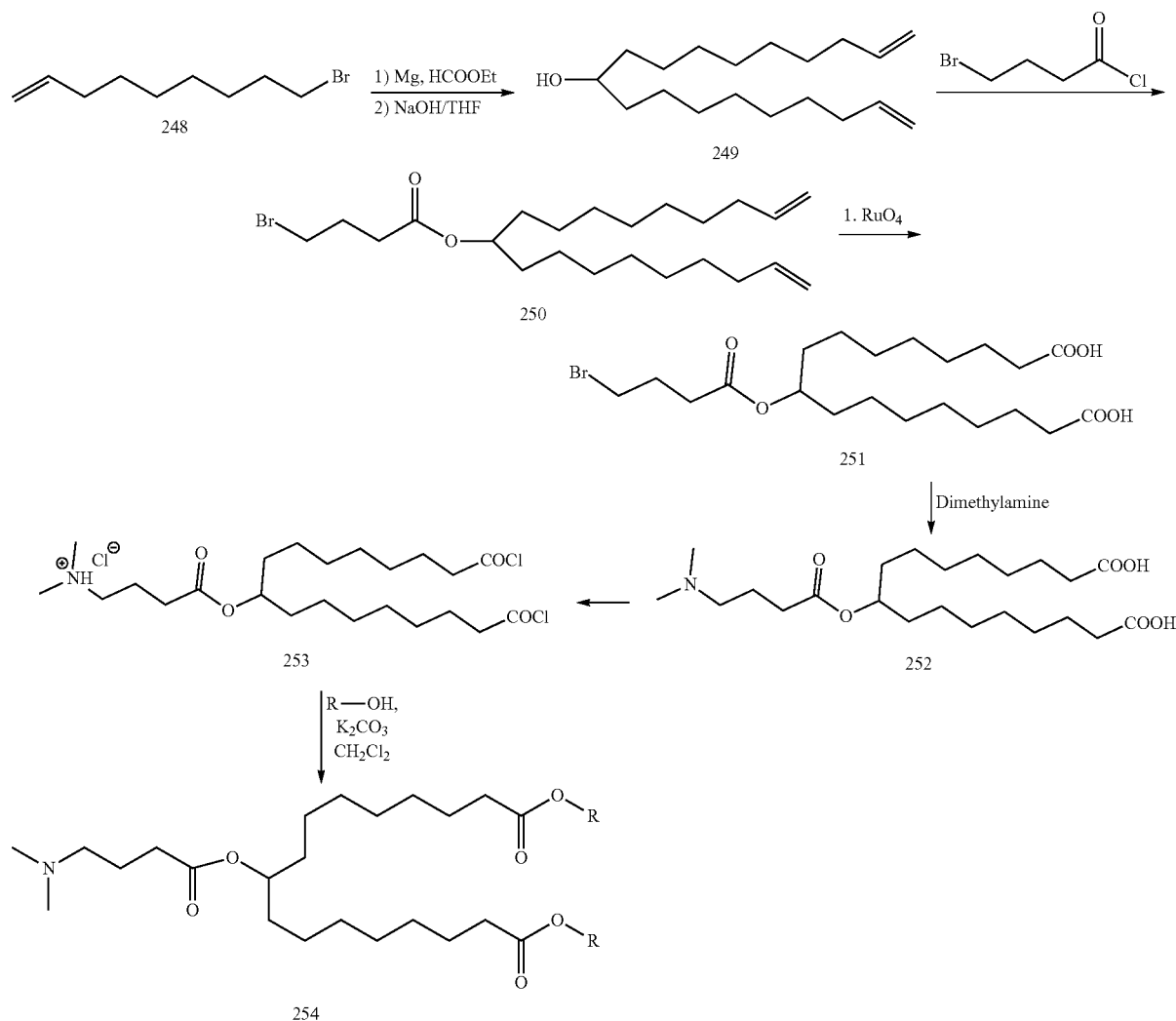
452

123.35, 74.12, 60.18, 58.95, 45.46, 34.30, 34.11, 32.45, 31.67, 29.38, 29.35, 29.17, 29.07, 28.84, 27.53, 25.28, 24.93, 23.16, 22.59, 14.06. MW calc. for C₄₁H₇₅NO₆ (MH⁺): 678.04, found: 678.5.

Example 18

The following shorter route was used for the synthesis of analogs of Compound 1 of the present invention. The commercial 9-bromonon-1-ene 248 was treated with magnesium to form the corresponding Grignard reagent which was reacted with ethylformate to give the corresponding adduct 249 which on treatment with bromobutyryl chloride to provide the bromoester 250. The bromoester 250 on treatment with RuO₄ provided the diacid 251. The bromodiacyd 251 on treatment with dimethylamine provided the amino diacid 252. The diacid 252 on treatment with oxalyl chloride in the presence of DMF provided the diacid chlorides 253. The lipids 254a-n were synthesized by treating the acid chloride 253 with respective alcohols.

Scheme 18



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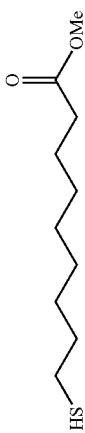
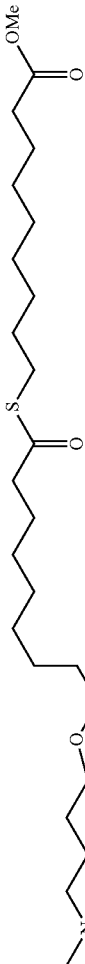

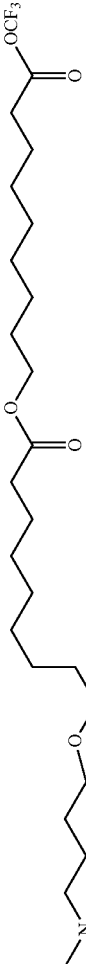

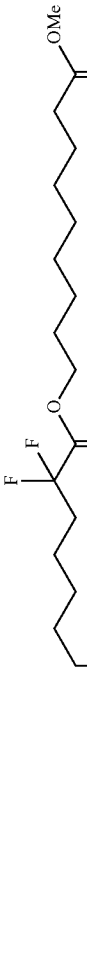
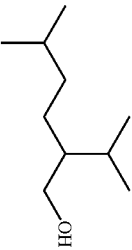
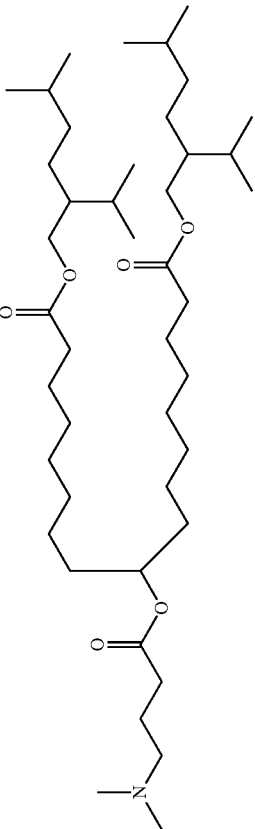
No	Starting Alcohol (ROH)	Product
254a		
254aS		
254aF		
254b		

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-continued

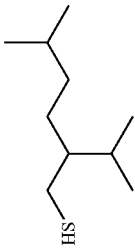
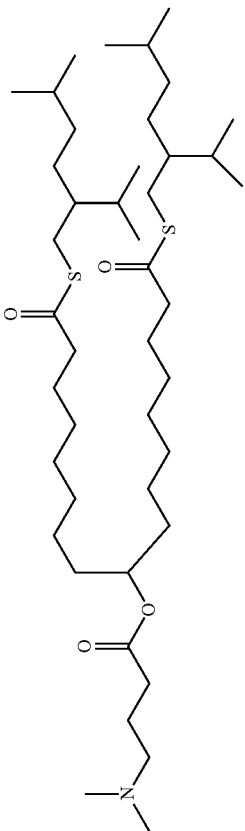
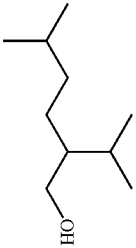
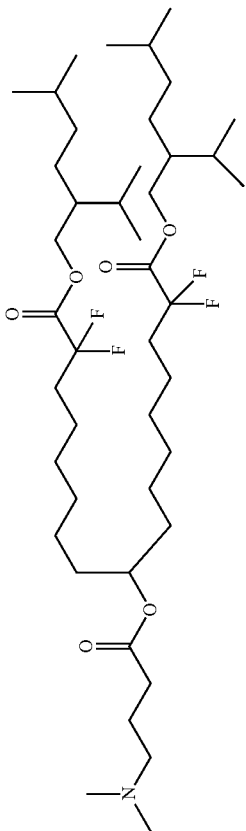

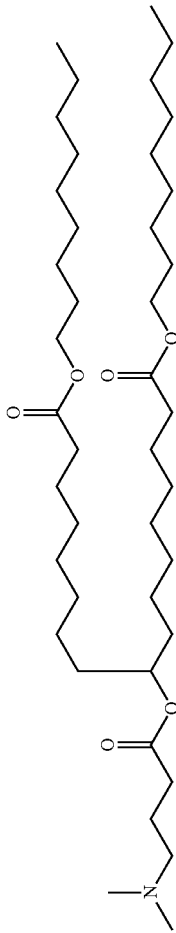

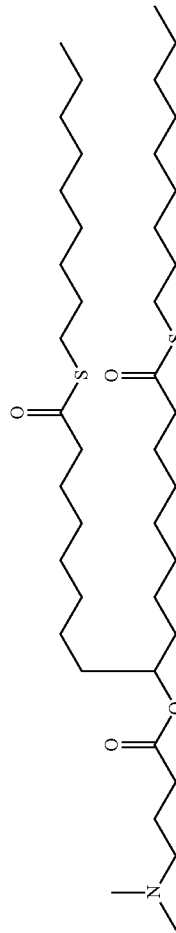
No	Starting Alcohol (ROH)	Product
254bS		
254bF		
254bF2		
254c		

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-continued

No	Starting Alcohol (ROH)	Product
254cS		
254cF		
254d		
254ds		

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-continued

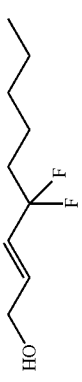
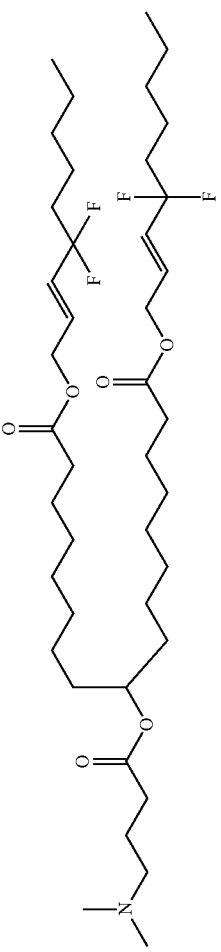
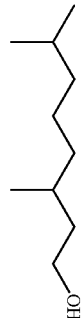
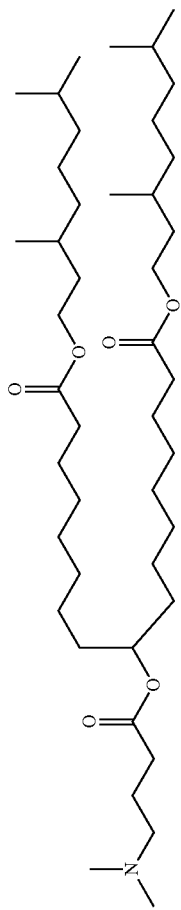
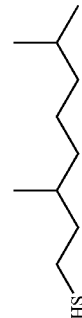
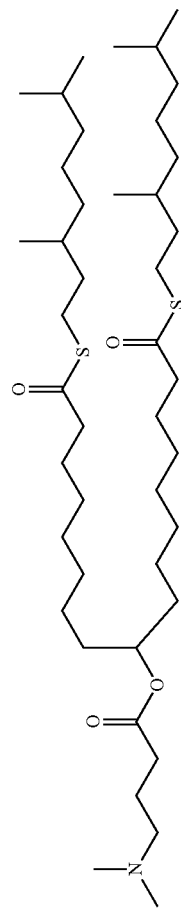
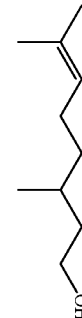
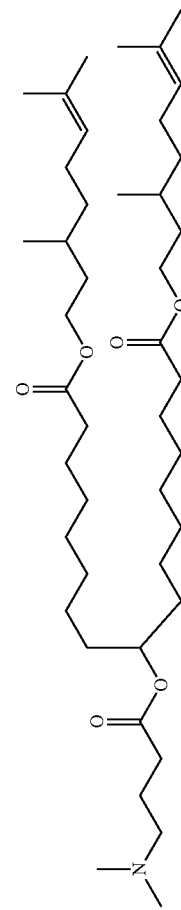
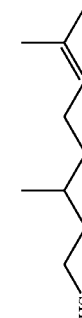
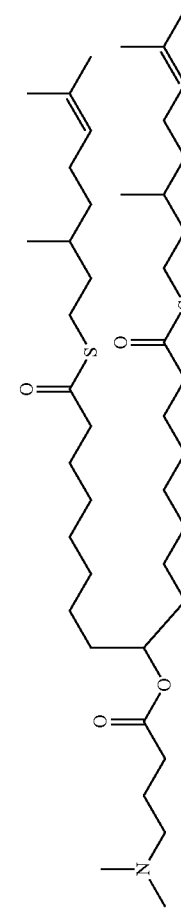
No	Starting Alcohol (ROH)	Product
254e		
254es		
254ef		
254f		
254fs		

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-continued

No	Starting Alcohol (ROH)	Product
254fF		
254g		
254gs		
254h		
254hs		

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464

-continued

No	Starting Alcohol (ROH)	Product
254hF		
254i		
254is		
254iF		
254j		

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465

466

-continued

No	Starting Alcohol (ROH)	Product
254js		
254jf		
254k		
254ks		
254ks		

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468

-continued

No	Starting Alcohol (ROH)	Product
254I		
254IF		
254m		
254ms		

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-continued

No	Starting Alcohol (ROH)	Product
2541s		
2540s		

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Synthesis of nonadeca-1,18-dien-10-ol (249)

To a flame dried 500 mL RB flask, freshly activated Mg turnings (9 g) were added and the flask was equipped with a magnetic stir bar, an addition funnel and a reflux condenser. This set-up was degassed and flushed with argon and 100 mL of anhydrous ether was added to the flask via syringe. The bromide 3 (51.3 g, 250 mmol) was dissolved in anhydrous ether (100 mL) and added to the addition funnel. About 5 mL of this ether solution was added to the Mg turnings while stirring vigorously. An exothermic reaction was noticed (to confirm/accelerate the Grignard reagent formation, 5 mg of iodine was added and immediate decolorization was observed confirming the formation of the Grignard reagent) and the ether started refluxing. The rest of the solution of the bromide was added dropwise while keeping the reaction under gentle reflux by cooling the flask in water. After the completion of the addition the reaction mixture was kept at 35° C. for 1 hour and then cooled in ice bath. Ethyl formate (9 g, 121 mmol) was dissolved in anhydrous ether (100 mL) and transferred to the addition funnel and added dropwise to the reaction mixture with stirring. An exothermic reaction was observed and the reaction mixture started refluxing. After the initiation of the reaction the rest of the ethereal solution of formate was quickly added as a stream and the reaction mixture was stirred for a further period of 1 h at ambient temperature. The reaction was quenched by adding 10 mL of acetone dropwise followed by ice cold water (60 mL). The reaction mixture was treated with aq. H₂SO₄ (10% by volume, 300 mL) until the solution became homogeneous and the layers were separated. The aq. phase was extracted with ether (2×200 mL). The combined ether layers were dried (Na₂SO₄) and concentrated to afford the crude product which was purified by column (silica gel, 0-10% ether in hexanes) chromatography. The product fractions were evaporated to provide the pure product 249 as a white solid (30.6 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 7.26 (s, 1H), 5.81 (ddt, J=16.9, 10.2, 6.7 Hz, 8H), 5.04-4.88 (m, 16H), 3.57 (dd, J=7.6, 3.3 Hz, 4H), 2.04 (q, J=6.9 Hz, 16H), 1.59 (s, 1H), 1.45 (d, J=7.5 Hz, 8H), 1.43-1.12 (m, 94H), 0.88 (t, J=6.8 Hz, 2H). ¹³C NMR (101 MHz, cdcl₃) δ 139.40, 114.33, 77.54, 77.22, 76.90, 72.21, 37.70, 34.00, 29.86, 29.67, 29.29, 29.12, 25.85.

Synthesis of nonadeca-1,18-dien-10-yl
4-bromobutanoate (250)

To a solution of the alcohol 249 (5.6 g, 20 mol) in anhydrous DCM (300 mL) was added slowly and carefully Bromobutryl chloride (20 mmol) at 0° C. under inert atmosphere. The reaction mixture was warmed to room temperature, stirred for 20 h and monitored by TLC (silica gel, 10% ethyl acetate in hexanes). Upon completion of the reaction, mixture was diluted with water (400 mL) and organic layer was separated out. Organic phase was then washed with sat. solution of NaHCO₃ (1×400 mL) followed by brine (1×100 mL) and concentrated under vacuum. Crude product was then purified by silica gel (100-200 mesh) column, eluted with 2-3% ethyl acetate in hexane solution to give 6 g (90%) of desired product 250 as colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, J=16.9, 10.2, 6.7 Hz, 2H), 5.05-4.81 (m, 5H), 3.46 (t, J=6.5 Hz, 2H), 2.48 (t, J=7.2 Hz, 2H), 2.17 (p, J=6.8 Hz, 2H), 2.11-1.93 (m, 4H), 1.65-1.44 (m, 4H), 1.43-1.17 (m, 19H). ¹³C NMR (101 MHz, cdcl₃) δ

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172.51, 139.37, 114.35, 77.54, 77.23, 76.91, 74.86, 34.31, 33.99, 33.01, 32.96, 29.65, 29.56, 29.24, 29.09, 28.11, 25.52.

Synthesis of
9-((4-bromobutanoyl)oxy)heptadecanedioic acid
(251)

To a solution of the bromoester 250 (12.1 g, 28.2 mmol) in dichloromethane (300 mL) and acetonitrile (300 mL), RuCl₃ (1.16 g, 5 mol %) was added and the mixture was cooled to 10° C. and sodium metaperiodate (60 g) in water (400 mL) was added dropwise. It was stirred at 10° C. for 20 hr. The reaction mixture was diluted with water, The layers were separated and to the organic layer, was added saturated brine solution with stirring followed by 3% sodium sulfide solution drop wise for the decolourisation (dark green to pale yellow). The layers were separated, the organic layer was dried over sodium sulfate and evaporated at reduced pressure to afford pure product. MW calcd for C₂₀H₃₅BrO₇ 467.39; Found 465.4 (M-2H). ¹H NMR (400 MHz, DMSO) δ 11.94 (s, 2H), 4.88-4.69 (m, 1H), 3.53 (t, J=6.6 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.17 (t, J=7.4 Hz, 4H), 2.09-1.95 (m, 2H), 1.90 (s, 3H), 1.46 (s, 7H), 1.23 (s, 15H).

Synthesis of
9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioic
acid (252)

The Bromoacid 251 (2 mmol) is dissolved in 2M solution of dimethylamine in THF (20 mL) and to it 1 g of anhydrous K₂CO₃ was added and the mixture was heated in a pressure bottle at 50° C. overnight. The TLC showed the completion of the reaction. The reaction mixture was acidified with acetic acid and diluted with water (100 mL) and extracted with dichloromethane (2×60 mL). The combined organic layers were concentrated dried and used as such in the next reaction. MW calcd for C₂₃H₄₃NO₆ 429.59; Found 430.6 (MH)⁺. ¹H NMR (400 MHz, DMSO) δ 11.87-11.82 (m, 7H), 5.75 (d, J=0.7 Hz, 15H), 4.85-4.69 (m, 38H), 3.64-3.55 (m, 12H), 3.35-2.83 (m, 106H), 3.01-2.90 (m, 59H), 2.94 (ddd, J=30.6, 7.7, 4.0 Hz, 63H), 2.90-2.73 (m, 9H), 2.70 (s, 221H), 2.57-2.46 (m, 91H), 2.44-2.30 (m, 76H), 2.17 (t, J=7.3 Hz, 147H), 1.89 (tq, J=15.5, 7.6 Hz, 88H), 1.79-1.69 (m, 13H), 1.65-1.32 (m, 311H), 1.28 (d, J=46.0 Hz, 598H).

Synthesis of
9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioyl
chloride (253)

The diacid 252 is converted to the corresponding diacid chloride 253 by treating it with oxalyl chloride in dichloromethane in the presence of catalytic DMF and the crude acid chloride obtained after the concentration of the reaction mixture was used as such for the coupling with different alcohols.

General Procedure for the Synthesis of Cationic
Lipids 254a-n

To a solution of the acid chloride 253 (500 mg, 1 mmol) in dichloromethane (30 mL) the corresponding alcohol (5 equivalent) was added at room temperature followed by solid K₂CO₃ (1 g) and the solution was stirred for 16 h at room temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed with satd. NaHCO₃ (100 mL) and the organic layer was dried (Anhyd. Na₂SO₄)

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and concentrated to obtain the crude product which was purified by Combiflash Rf purification system.

Compound 254b: By using the above procedure the lipid 254b was isolated in 72% yield (554 mg). ¹H NMR (400 MHz, CDCl₃) δ 4.91-4.78 (m, 1H), 4.05 (t, J=6.7 Hz, 4H), 3.81 (s, 6H), 3.63 (t, J=6.4 Hz, 1H), 2.29 (dt, J=15.2, 7.5 Hz, 8H), 2.21 (s, 6H), 1.84-1.69 (m, 2H), 1.57 (dt, J=13.4, 5.2 Hz, 9H), 1.53-1.40 (m, 4H), 1.27 (s, 43H). ¹³C NMR (101 MHz, cdcl₃) δ 174.45, 174.13, 173.59, 77.54, 77.22, 76.91, 74.34, 64.54, 59.17, 51.65, 45.67, 34.56, 34.35, 34.27, 32.67, 29.59, 29.40, 29.33, 29.31, 29.25, 28.83, 26.06, 25.51, 25.18, 25.11, 23.38. MW calcd for C₄₃H₇₉NO₁₀ 770.09; Found 770.68.

Compound 254c: By using the above procedure the lipid 254c was isolated in 69% (490 mg). ¹H NMR (400 MHz, CDCl₃) δ 5.71-5.36 (m, 4H), 4.89-4.72 (m, 1H), 4.59 (d, J=6.8 Hz, 4H), 2.26 (ddd, J=22.3, 13.0, 8.6 Hz, 9H), 2.19 (s, 6H), 2.12-1.95 (m, 4H), 1.82-1.68 (m, 2H), 1.63-1.37 (m, 8H), 1.37-1.00 (m, 32H), 0.85 (t, J=6.8 Hz, 6H). ¹³C NMR (101 MHz, cdcl₃) δ 173.94, 173.57, 135.61, 123.57, 77.54, 77.22, 76.91, 74.34, 60.40, 59.16, 45.65, 34.52, 34.33, 32.66, 31.88, 29.59, 29.57, 29.38, 29.28, 29.06, 27.75, 25.49, 25.14, 23.35, 22.81, 14.28. MW calcd for C₄₃H₈₃NO₆: 710.12; Found 710.81.

Compound 254d: By using the above procedure the lipid 254d was isolated in 67% yield (456 mg). ¹H NMR (400 MHz, CDCl₃) δ 4.92-4.78 (m, 1H), 4.05 (t, J=6.7 Hz, 4H), 3.63 (t, J=6.4 Hz, 1H), 2.39-2.24 (m, 8H), 2.21 (s, 6H), 1.89-1.70 (m, 2H), 1.69-1.54 (m, 8H), 1.51 (dd, J=17.2, 6.3 Hz, 4H), 1.27 (s, 42H), 0.88 (t, J=6.8 Hz, 6H). MW calcd for: C₄₁H₇₉NO₆: 682.07; Found 682.96.

Compound 254e: By using the above procedure the lipid 254e was isolated in 70% (474 mg). ¹H NMR (400 MHz,

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CDCl₃) δ 5.49 (ddd, J=12.9, 9.8, 7.3 Hz, 2H), 5.40-5.23 (m, 2H), 4.92-4.77 (m, 1H), 4.05 (t, J=6.9 Hz, 4H), 2.32 (ddd, J=23.4, 14.5, 7.1 Hz, 12H), 2.21 (s, 6H), 2.07-1.91 (m, 4H), 1.84-1.70 (m, 2H), 1.66-1.39 (m, 8H), 1.40-1.15 (m, 26H), 0.88 (t, J=6.8 Hz, 5H). MW calc. for C₄₁H₇₅NO₆ (MH⁺): 678.04, found: 678.5.

Compound 254f: By using the above procedure the lipid 254f was isolated in 73% (559 mg). ¹H NMR (400 MHz, CDCl₃) δ 5.87-5.62 (m, 2H), 5.55 (dt, J=9.1, 6.4, 1.3 Hz, 2H), 4.93-4.75 (m, 1H), 4.50 (dd, J=6.5, 0.6 Hz, 4H), 2.40-2.17 (m, 13H), 2.12-1.95 (m, 4H), 1.89-1.67 (m, 2H), 1.69-1.44 (m, 7H), 1.41-1.12 (m, 25H), 0.88 (t, J=6.9 Hz, 5H). MW calc. for C₄₁H₇₅NO₆ (MH⁺): 678.04, found: 678.5.

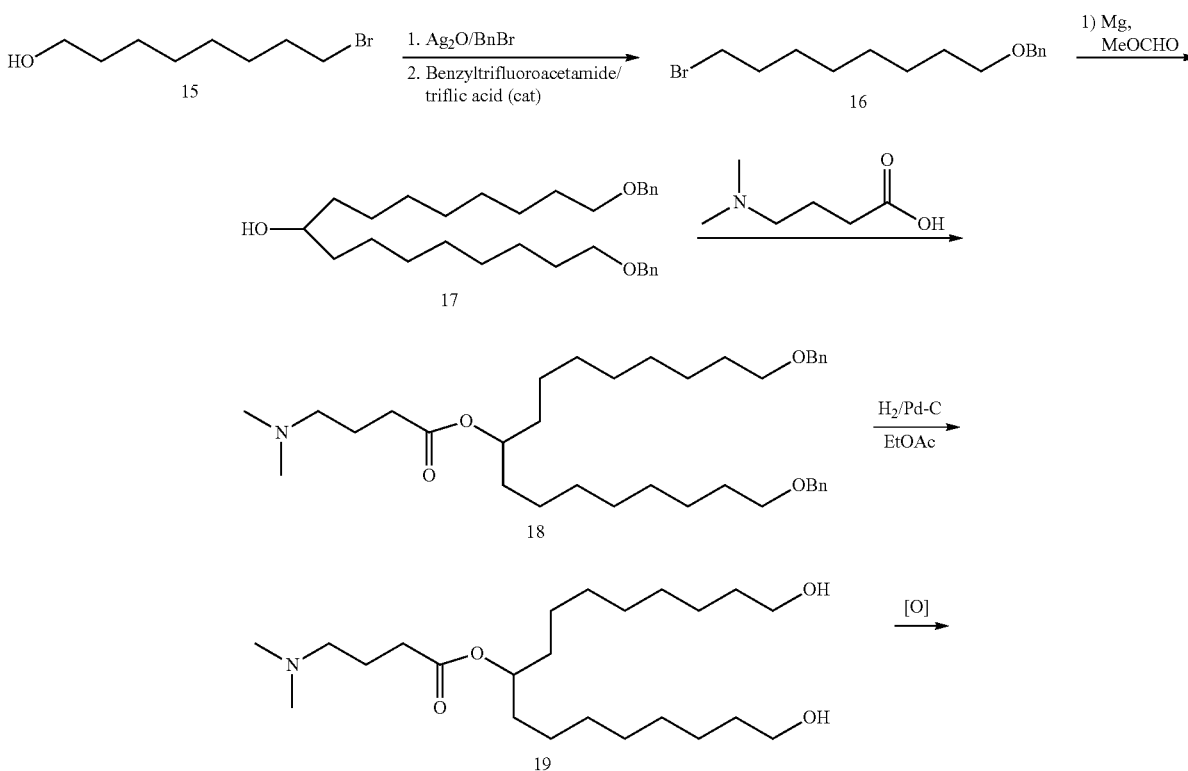
Compound 254g: By using the above procedure the lipid 254g was isolated in 63% (432 mg). ¹H NMR (400 MHz, CDCl₃) δ 4.93-4.77 (m, 1H), 4.20-3.95 (m, 4H), 2.44-2.23 (m, 8H), 2.21 (s, 6H), 1.84-1.66 (m, 3H), 1.68-1.34 (m, 15H), 1.35-1.17 (m, 20H), 1.17-1.04 (m, 5H), 0.88 (dd, J=12.4, 6.6 Hz, 16H). MW calcd for C₄₃H₈₃NO₆: 710.12; Found 710.81.

Compound 254h: By using the above procedure the lipid 254h was isolated in 66% (466 mg). ¹H NMR (400 MHz, CDCl₃) δ 5.08 (ddd, J=7.1, 5.9, 1.3 Hz, 2H), 4.91-4.75 (m, 1H), 4.22-3.97 (m, 4H), 2.39-2.22 (m, 8H), 2.23 (d, J=16.7 Hz, 7H), 2.09-1.84 (m, 4H), 1.86-1.71 (m, 3H), 1.71-1.02 (m, 44H), 0.91 (t, J=4.9 Hz, 6H). MW calcd for C₄₃H₇₉NO₆: 706.12; Found 706.81.

Example 19

In another approach the following synthetic approach is used for the synthesis of Compound 1 of the present invention.

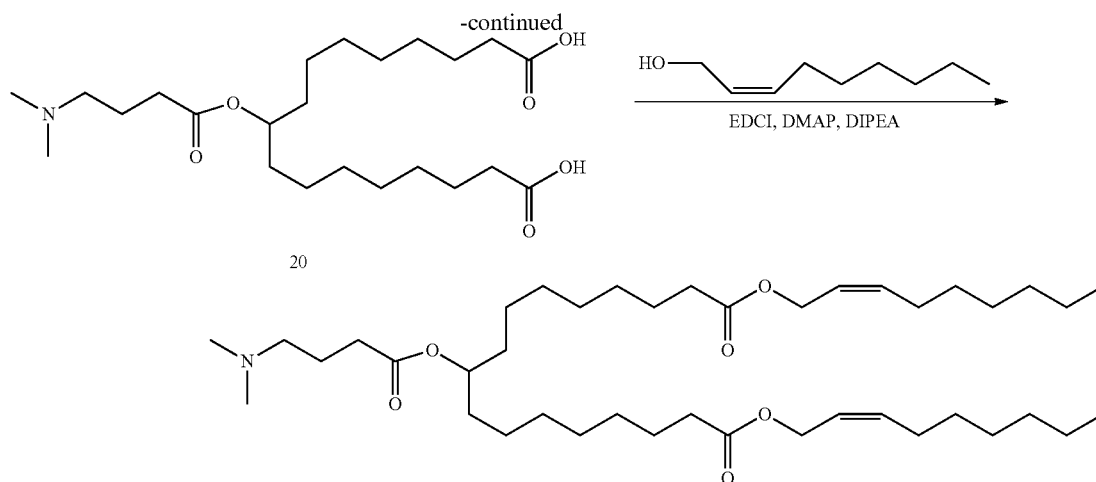
Scheme 19



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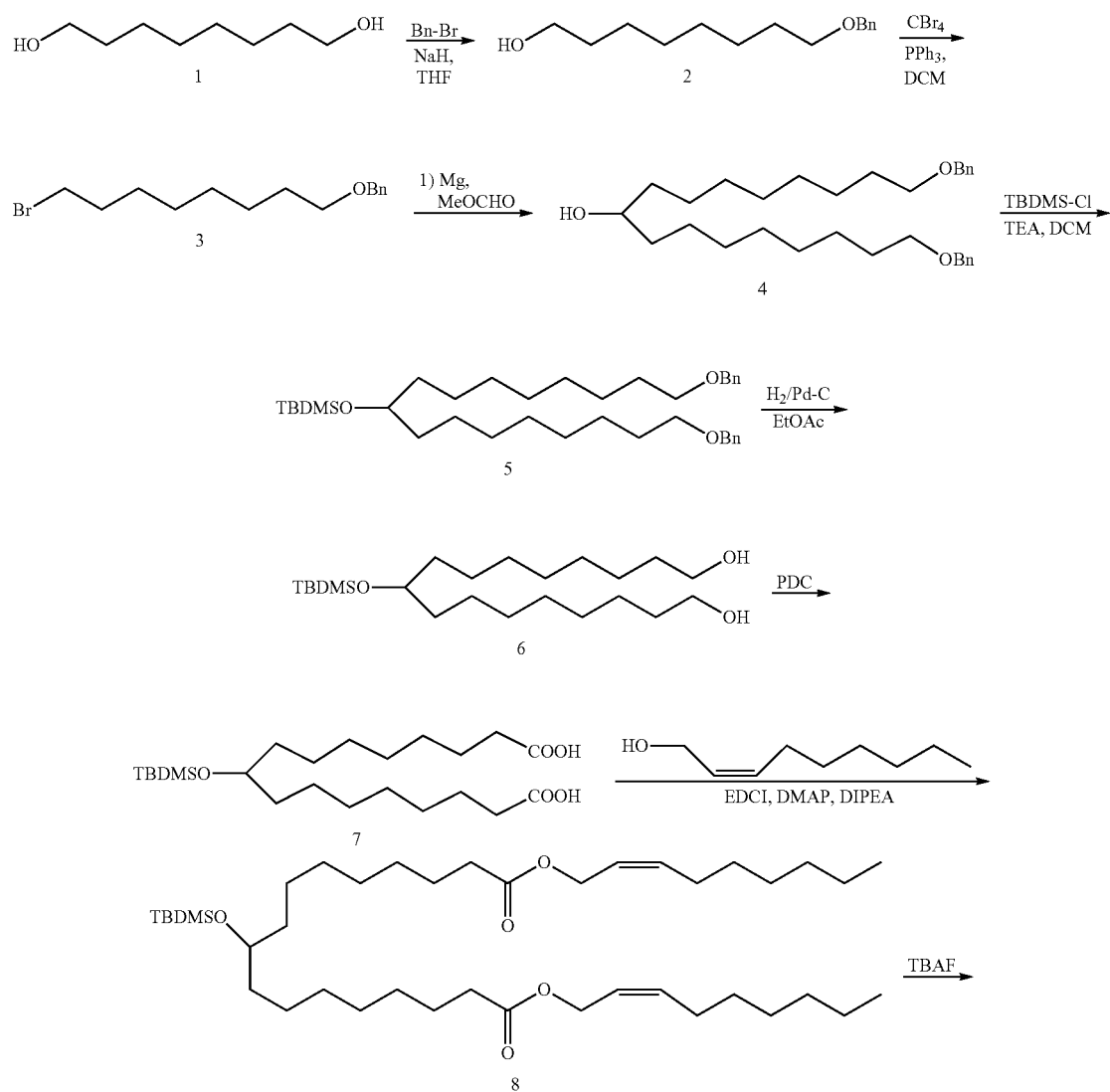
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Example 20

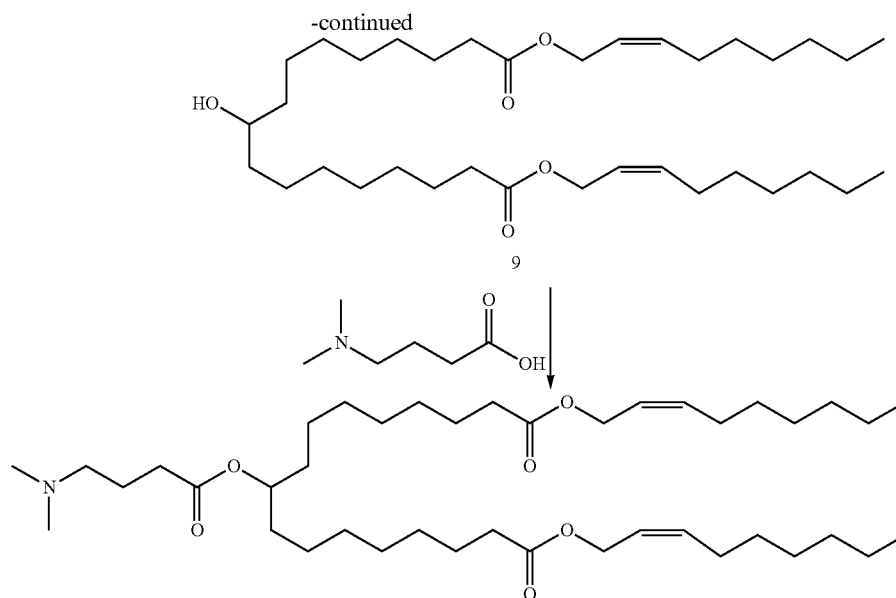
Scheme 20



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8-benzyloxy-octan-1-ol (2): To a stirred suspension of NaH (60% in oil, 82 g, 1.7096 mol) in 500 mL anhydrous DMF, a solution of compound 1 (250 g, 1.7096 mol) in 1.5 L DMF was added slowly with dropping funnel at 0° C. Reaction mixture was stirred for 30 min and to it Benzyl bromide (208.86 mL, 1.7096 mol) was added slowly under nitrogen atmosphere. Reaction was then warmed to ambient temperature and stirred for 10 h. After completion of reaction, mixture was quenched with crushed ice (~2 kg) and extracted with Ethyl acetate (2×1 L). Organic layer washed with water (1 L) to remove unwanted DMF, dried over Na₂SO₄ and evaporated to dryness under vacuum. The crude compound was purified on 60-120 silica gel, eluted with 0-5% MeOH in DCM to afford compound 2 (220 g, 54%) as pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 5H), 4.49 (s, 2H), 3.63-3.60 (m, 2H), 3.47-3.43 (m, 2H), 1.63-1.51 (m, 4H), 1.39-1.23 (m, 8H).

(8-bromo-octyloxymethyl)-benzene (3): Compound 2 (133 g, 0.5635 mol) was dissolved in 1.5 L of DCM, CBr₄ (280.35 g, 0.8456 mol) was added into this stirring solution and reaction mixture was cooled to 0° C. under inert atmosphere. PPh₃ (251.03 g, 0.9571 mol) was then added in portions keeping the temperature below 20° C. and after complete addition reaction was stirred for 3 h at room temperature and monitored by TLC. After completion of reaction, solid (PPh₃O) precipitated out from the reaction mixture was filtered off and filtrate was diluted with crushed ice (~1.5 kg) and extracted with DCM (3×750 mL). Organic layer was separated, dried over an. Na₂SO₄ and distilled under vacuum. Resulting crude compound was chromatographed on 60-120 mesh silica gel column using 0-5% ethyl acetate in hexanes as eluting system to give compound (150 g, 89%) as pale yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.47-3.41 (m, 2H), 3.41-3.37 (m, 2H), 1.86-1.80 (m, 4H), 1.62-1.56 (m, 2H), 1.42-1.29 (m, 8H).

1, 17-bis-benzyloxy-heptadecan-9-ol (4): To freshly activated Mg turnings (24.08 g, 1.003 mol) was added 200 mL anhydrous THF was added followed by the addition of pinch of iodine into the mixture under inert atmosphere. After

initiation of the Grignard formation a solution of Compound 3 (150 g, 0.5016 mol) in 1 L of dry THF was added slowly controlling the exothermic reaction. After complete addition reaction was refluxed for 1 h and then cooled to room temperature. (60.24 g, 1.0033 mol) methyl formate was then added slowly and reaction was continued for 2 h. After completion, the reaction was quenched by slow addition of 10% HCl followed by water (1 L) and extracted with Ethyl Acetate (3×1 L). Organic layer was taken in 5 lit beaker, diluted with 500 mL of methanol and cooled to 0° C. To this solution excess of NaBH₄ (~5 eq) was added in portions to ensure the hydrolysis of formate ester which was not cleaved by addition of HCl. Resulting solution was stirred for an hour and then volatiles were stripped off under vacuum. Residue was taken in water (1 L) and acidified by 10% HCl solution (pH 4).

Product was then extracted out with ethyl acetate (3×1 L). Organic phase was then dried and concentrated on rotary evaporator to get the desired compound 4 (57 g, 24%) as solid. ¹H NMR (400 MHz, CDCl₃): δ=7.35-7.32 (m, 8H), 7.29-7.24 (m, 2H), 4.49 (s, 4H), 3.56 (m, 1H), 3.46-3.43 (m, 4H), 1.63-1.56 (m, 4H), 1.44-1.34 (m, 28H). C¹³ NMR (100 MHz, CDCl₃): δ=138.56, 128.21, 127.49, 127.34, 72.72, 71.76, 70.37, 37.37, 29.64, 29.56, 29.47, 29.33, 26.07, 25.54.

[9-benzyloxy-1-(8-benzyloxy-octyl)-nonyloxy]-tert-butyl-dimethyl-silane (5): Compound 4 (56 g, 0.1196 mol) was dissolved in 700 mL of anhydrous THF and cooled to 0° C. TBMS-Cl (36.06 g, 0.2396 mol) was added slowly followed by addition of Imidazole (32.55 g, 0.4786 mol) under inert atmosphere. Reaction was then stirred at room temperature for 18 h. Reaction was judged complete by TLC and then quenched with ice (~1 kg) and extracted with Ethyl acetate (3×500 mL). Organic layer was separated, washed with Sat NaHCO₃ solution to remove the acidic impurity, dried over Na₂SO₄ and evaporated under reduce pressure to obtain crude compound which was purified by silica gel (60-120 mesh) and eluted with 0-10% ethyl acetate hexane to yield (60 g, 82%) of compound 5 as yellowish oil. ¹H NMR (400 MHz, CDCl₃): δ=7.33-7.24 (m, 10H), 4.49 (s,

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4H), 3.60-3.57 (m, 1H), 3.46-3.43 (m, 4H), 1.61-1.54 (m, 4H), 1.41-1.26 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H)

9-(tert-butyl-dimethyl-silanyloxy)-heptadecane-1,17-diol (6): Compound 5 (60 g, 0.1030 mol) was dissolved in 500 mL ethyl acetate and degassed with N₂ for 20 min. (10 wt %) Pd on carbon (12 g) was added and reaction was stirred under H₂ atmosphere for 18 h. After completion of reaction (by TLC) mixture was filtered through celite bed and washed with ethyl acetate. Filtrate was evaporated under vacuum. The compound 6 (19 g, 46%) thus obtained was pure enough to carry out the next reaction. ¹H NMR (400 MHz, CDCl₃): δ=3.64-3.58 (m, 5H), 1.59 (br, 2H), 1.57-1.51 (m, 4H), 1.38-1.22 (m, 28H), 0.87 (s, 9H), 0.02 (s, 6H).

9-(tert-butyl-dimethyl-silanyloxy)-heptadecanedioic acid (7): To a stirred solution of 6 (2 g, 0.0049 mol) in anhydrous DMF (40 mL) was added pyridinium dichromate (2.7 g, 0.0074 mol) at 0° C. under inert atmosphere. Reaction mixture was then allowed to warm to room temperature over a period of 10-15 minutes and continued for 24 h. Progress of the reaction was monitored by TLC. After complete oxidation reaction was diluted with water (100 mL). Aqueous phase was extracted with DCM (3×40 mL). Organic phase was washed with brine (1× 25 mL) and concentrated under vacuum to afford crude acid which was then purified by (100-200 mesh) silica gel column using 0-30% ethyl acetate in hexanes system. Pure product 26-003 was obtained (0.7 g, 33%) as pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ=3.61-3.56 (m, 1H), 2.35-2.32 (m, 4H), 1.64-1.59 (m, 4H), 1.40-1.19 (m, 24H), 0.86 (s, 9H), 0.017 (s, 6H); LC-MS [M+H]⁺=431.00; HPLC (ELSD) purity ~96.94%

Di((Z)-non-2-en-1-yl) 9-((tert-butyl dimethylsilyl)oxy) heptadecanedioate (8): The diacid 7 (0.42 g, 0.97 mmol) was dissolved in 20 mL of dichloromethane and to it cis-2-nonen-1-ol (0.35 g, 2.44 mmol) was added followed by Hunig's base (0.68 g, 4.9 mmol) and DMAP (12 mg). To this mixture EDCI (0.47 g, 2.44 mmol) was added and the reaction mixture was stirred at room temperature overnight and the TLC (silica gel, 5% MeOH in CH₂Cl₂) showed complete disappearance of the starting acid. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with saturated NaHCO₃ (50 mL), water (60 mL) and brine (60 mL). The combined organic layers were dried over anhyd. Na₂SO₄ and solvents were removed in vacuo. The crude product thus obtained was purified by Combiflash Rf purification system (40 g silicagel, 0-10% MeOH in CH₂Cl₂) to isolate the pure product 8 (0.35 g, 53%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ ¹H NMR (400 MHz, CDCl₃) δ 5.64 (dt, J=10.9, 7.4 Hz, 2H), 5.58-5.43 (m, 2H), 4.61 (d, J=6.8 Hz, 4H), 3.71-3.48 (m, 1H), 2.30 (t, J=7.6 Hz, 4H), 2.20-1.98 (m, 4H), 1.71-1.53 (m, 4H), 1.31 (ddd, J=8.3, 7.0, 3.7 Hz, 34H), 1.07-0.68 (m, 14H), 0.02 (s, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 178.18, 139.81, 127.78, 81.73, 81.42, 81.10, 76.72, 64.59, 41.52, 41.32, 38.76, 36.09, 34.10,

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33.93, 33.80, 33.70, 33.59, 33.55, 33.26, 31.95, 30.34, 29.69, 29.58, 29.39, 27.01, 22.56, 18.48, 0.01.

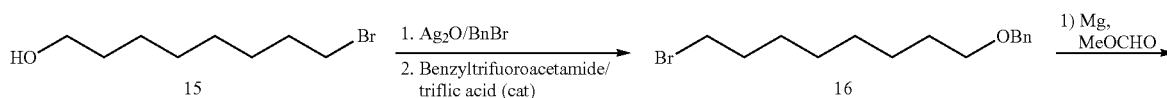
Di((Z)-non-2-en-1-yl) 9-hydroxyheptadecanedioate (9): The silyl protected diester 8 (0.3 g, 0.44 mmol) was dissolved in 1 M solution of TBAF in THF (6 mL) and the solution was kept at 40° C. for two days after which the TLC showed the completion of the reaction. The reaction mixture was diluted with water (60 mL) and extracted with ether (2×50 mL). The combined organic layers were concentrated and the thus obtained crude product was purified by column to isolate the pure product (0.097 g, 39%). ¹H NMR (400 MHz, CDCl₃) δ 5.64 (dt, J=10.9, 7.4 Hz, 2H), 5.52 (dt, J=11.0, 6.8 Hz, 2H), 4.61 (d, J=6.8 Hz, 4H), 3.57 (s, 1H), 2.30 (t, J=7.5 Hz, 4H), 2.09 (q, J=7.1 Hz, 4H), 1.75-1.53 (m, 4H), 1.53-1.06 (m, 36H), 0.88 (t, J=6.8 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 173.98, 135.64, 123.57, 77.54, 77.22, 76.91, 72.14, 60.41, 37.69, 34.54, 31.89, 29.70, 29.60, 29.44, 29.29, 29.07, 27.76, 25.80, 25.15, 22.82, 14.29.

Di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate: The alcohol 9 (0.083 g, 0.147 mmol) was dissolved in 20 mL of dichloromethane and to it dimethylaminobutyric acid hydrochloride (0.030 g, 0.176 mmol) was added followed by Hunig's base (0.045 g, 0.44 mmol) and DMAP (2 mg). To this mixture EDCI (0.034 g, 0.176 mmol) was added and the reaction mixture was stirred at room temperature overnight and the TLC (silica gel, 10% MeOH in CH₂Cl₂) showed complete disappearance of the starting alcohol. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with saturated NaHCO₃ (50 mL), water (60 mL) and brine (60 mL). The combined organic layers were dried over anhyd. Na₂SO₄ and solvents were removed in vacuo. The crude product thus obtained was purified by Combiflash Rf purification system (40 g silicagel, 0-10% MeOH in CH₂Cl₂) to isolate the pure product (0.062 g, 62%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.74-5.58 (m, 2H), 5.51 (dt, J=9.7, 6.8, 1.3 Hz, 2H), 4.95-4.75 (m, 1H), 4.61 (d, J=6.8 Hz, 4H), 2.35-2.24 (m, 8H), 2.22 (d, J=7.9 Hz, 6H), 2.09 (q, J=6.9 Hz, 4H), 1.83-1.72 (m, 2H), 1.60 (dd, J=14.4, 7.2 Hz, 4H), 1.49 (d, J=5.7 Hz, 4H), 1.41-1.13 (m, 30H), 0.88 (t, J=6.9 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 173.72, 173.36, 135.40, 123.35, 74.12, 60.18, 58.95, 45.46, 34.30, 34.11, 32.45, 31.67, 29.38, 29.35, 29.17, 29.07, 28.84, 27.53, 25.28, 24.93, 23.16, 22.59, 14.06. MW calc. for C₄₁H₇₅NO₆ (MH⁺): 678.04, found: 678.5.

In another embodiment the following shorter route was used for the synthesis of the di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate. The commercial 9-bromonon-1-ene 10 was treated with magnesium to form the corresponding Grignard reagent which was reacted with ethylformate to give the corresponding adduct 11 which on treatment with bromobutyl chloride to provide the bromoester 12. The bromoester 12 on treatment with RuO₄ provided the diacid 13. The bromodiacyd 13 on treatment with dimethylamine provided the amino diacyd 14. The aminodiacyd 14 on coupling with the alcohol 15 provided the product in good yields.

Example 21

Scheme 21

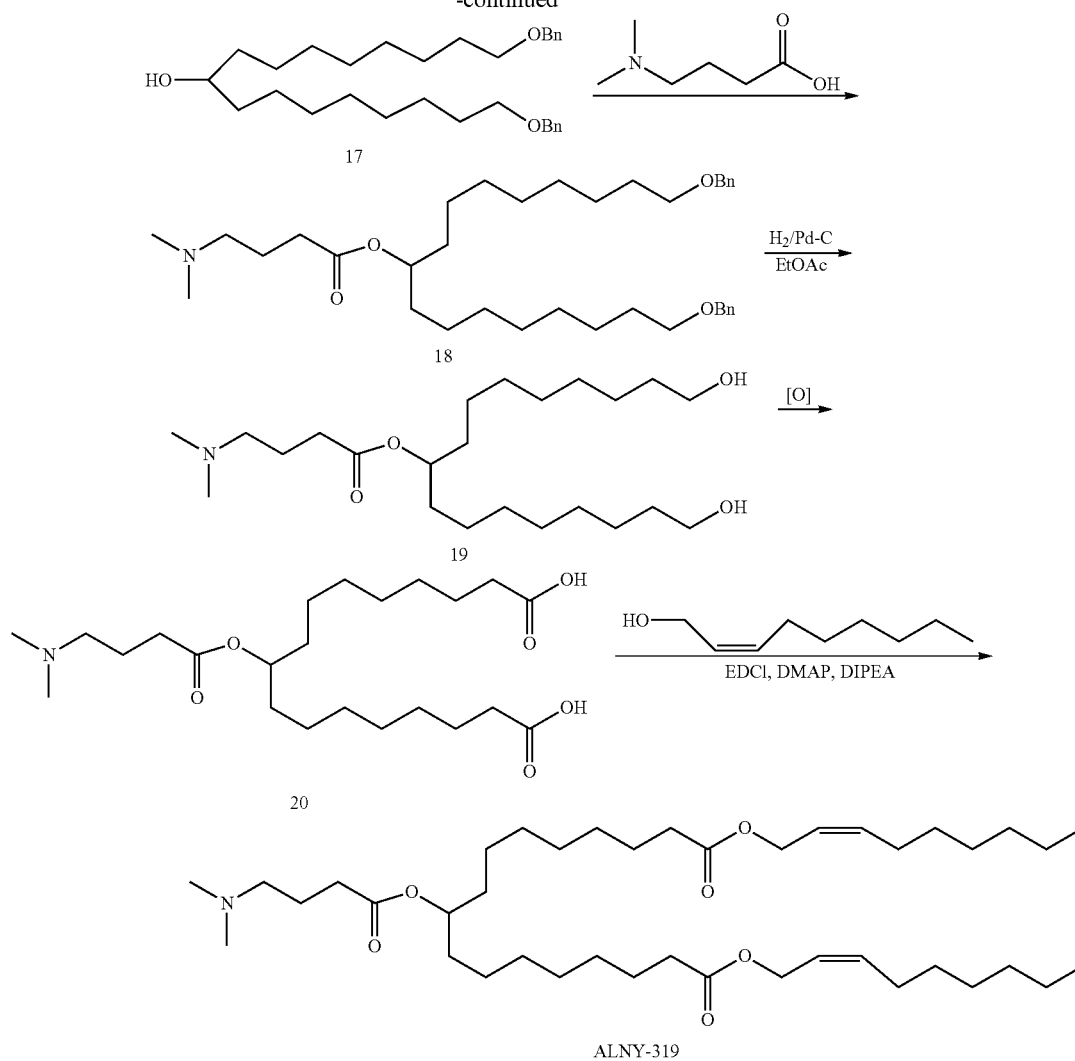


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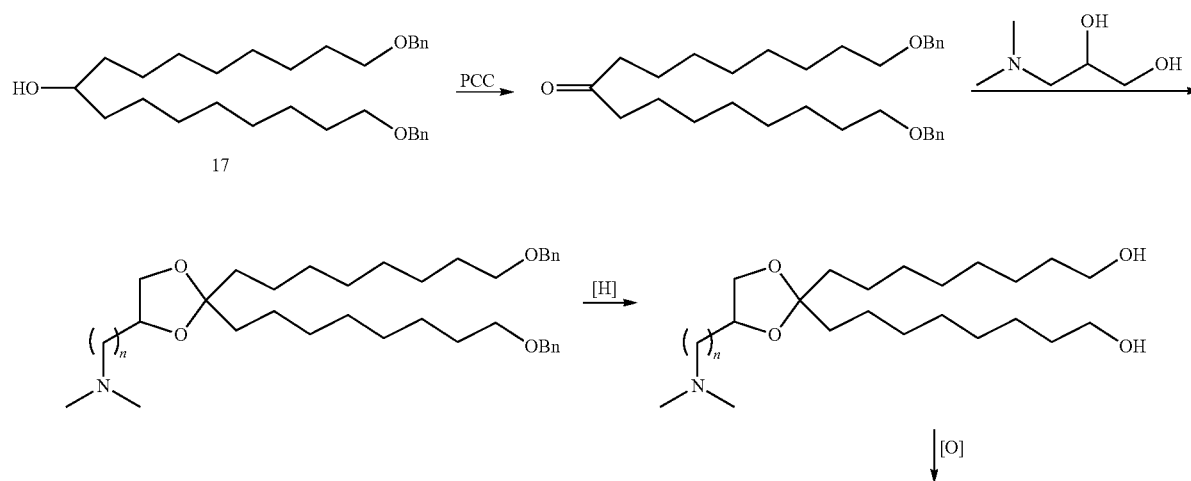
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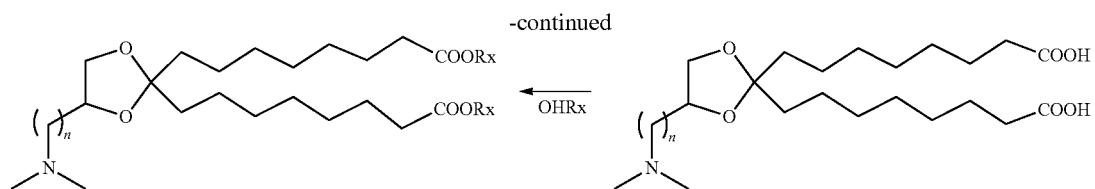


Example 22

Scheme 22



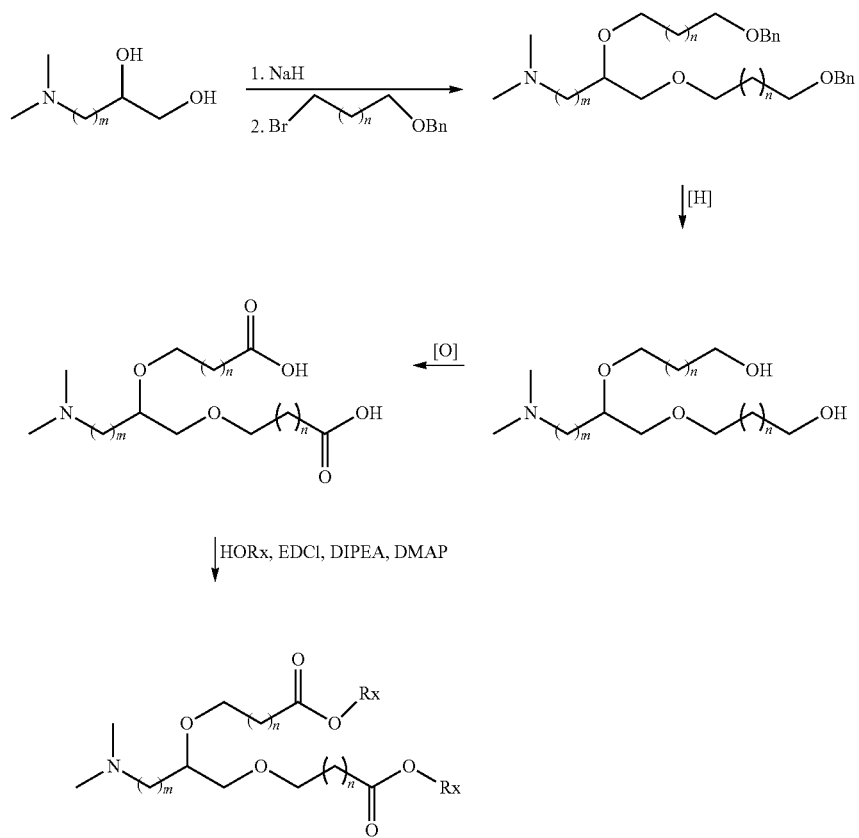
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Example 23

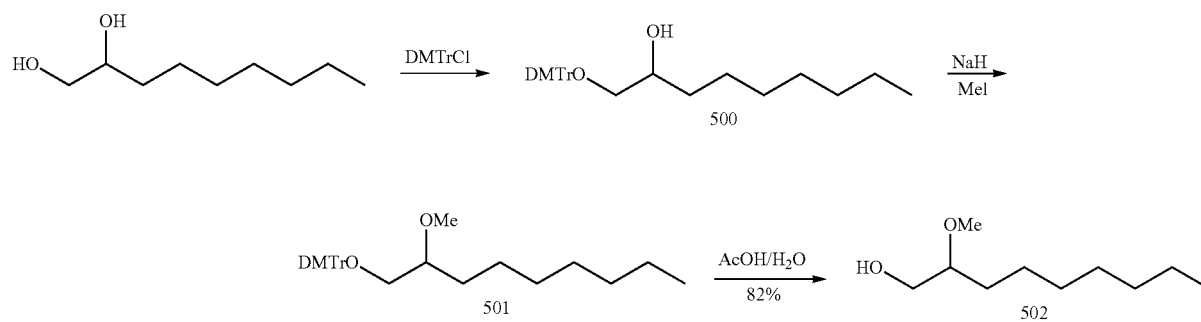
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Scheme 23

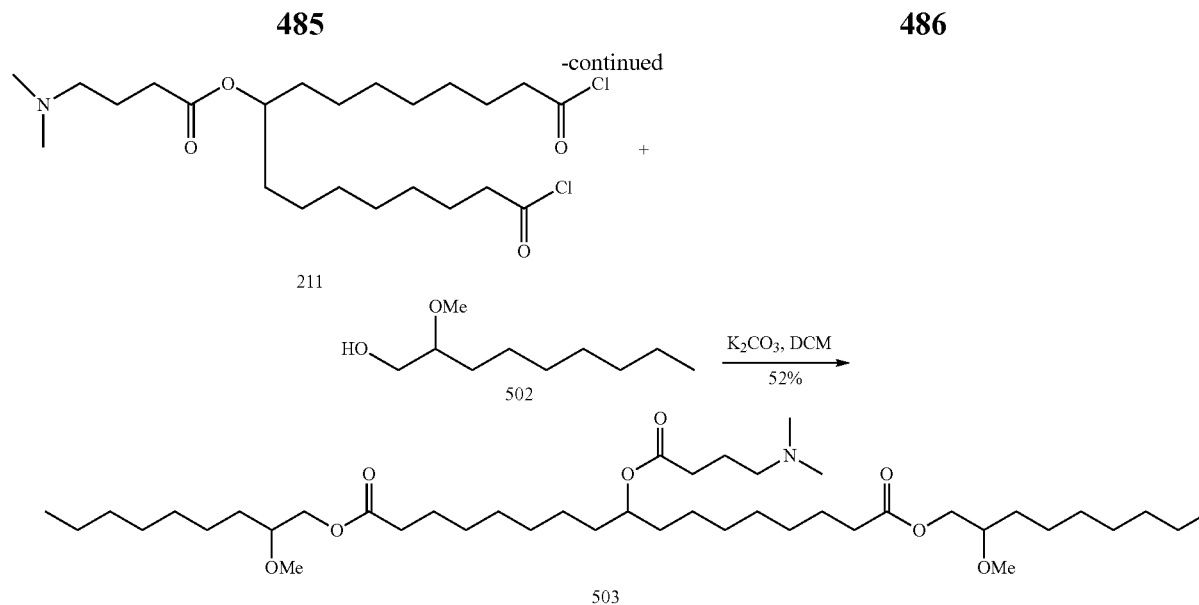


Example 24

Scheme 24



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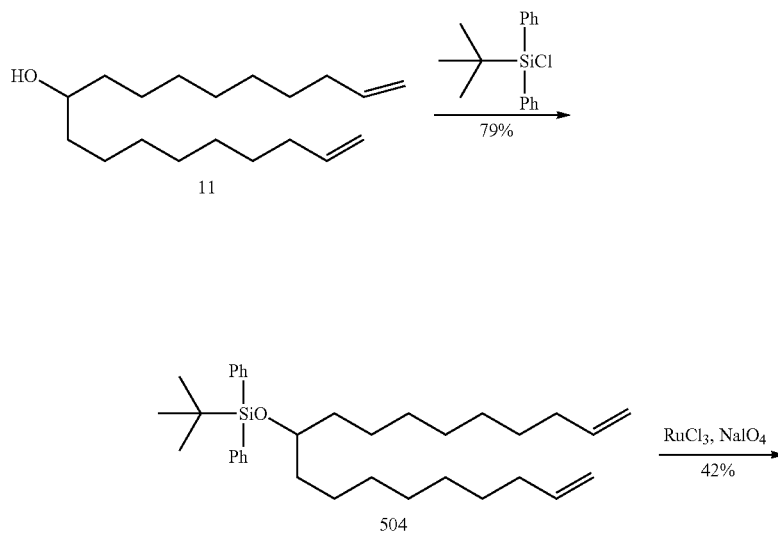
Compound 501: To a stirred solution of 2-hydroxy 1-octanol 5 g (31.25 mmol), DMAP 0.38 g (3.1 mmol) in dry pyridine (100 mL) was added DMTr-Cl and stirred at room temperature for 14 h. 10 mL of water was added and extracted with ethyl acetate, washed with saturated NaHCO_3 and brine. The organic layer was dried over Na_2SO_4 and concentration of the solvent gave 20 g of crude product 500 which was co-evaporated with toluene twice and used for the next step without further purification. To the above crude DMTr ether in dry THF (250 mL) were added NaH and iodo methane at 0°C . and then brought to room temperature over 30 min. and then stirred for two days. 5 mL of water was added and concentrated followed by column chromatography (0-30% ethyl acetate in hexane) gave the corresponding product 501 (10.25 g, R_f : 0.45, 20% ethyl acetate in hexane) and 8.4 g of recovered starting material 500. ^1H NMR (400 MHz, CDCl_3) δ 7.47-6.8 (m, 13H), 3.79 (s, 6H), 3.42 (s, 3H), 3.29-3.26 (m, 1H), 3.13-3.04 (m, 2H), 1.55-1.47 (m, 2H), 1.3-1.2 (m, 10H), 0.89 (t, $J=6.4$ Hz, 3H).

Alcohol 502: The compound 501 (10.25 g, 21.5 mmol) was dissolved in 75 mL of 80% acetic acid and stirred at room temperature for 14 h. 10 mL of methanol was added and concentrated, followed by column chromatography (0-50% ethyl acetate in hexane) yielded the expected product 502 as colorless oil (1.8 g, 82%, R_f : 0.3, 30% ethyl acetate in hexane). ^1H NMR (400 MHz, CDCl_3) δ 3.71-3.65 (m, 1H), 3.5-3.45 (m, 1H), 3.41 (s, 3H), 3.28-3.25 (m, 1H), 1.93-1.9 (m, 1H), 1.45-1.41 (m, 2H), 1.39-1.27 (m, 10H), 0.88 (s, $J=6.8$ Hz, 3H).

Compound 503: Compound 503 was synthesized following general experimental procedure for compound 213. 0.3 g as pale yellow oil (52%, $R_f=0.2$, 5% methanol in dichloromethane). ^1H NMR (400 MHz, CDCl_3) δ 4.87-4.84 (m, 1H), 4.18-4.00 (m, 4H), 3.4 (s, 6H), 3.37-3.19 (m, 2H), 2.34-2.26 (m, 6H), 2.2 (s, 6H), 1.8-1.6 (m, 2H), 1.63-1.2 (m, 50H), 0.88 (s, $J=6.8$ Hz, 6H).

Example 25

Scheme 25

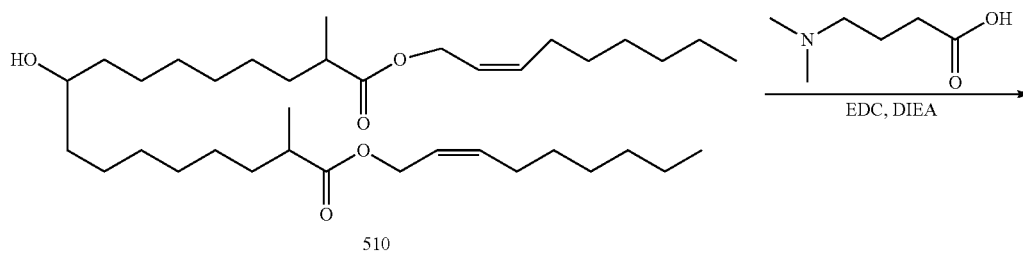
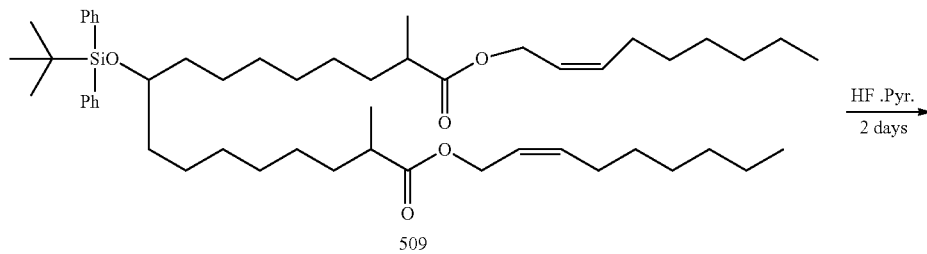
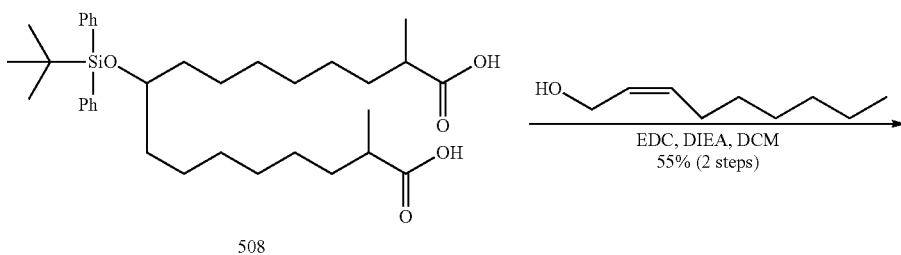
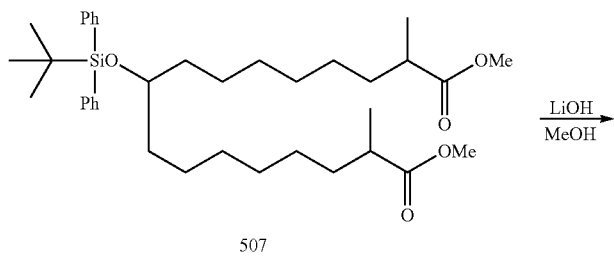
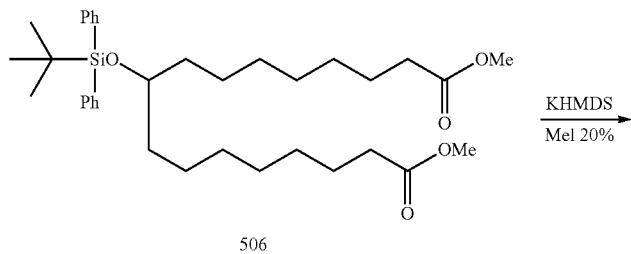
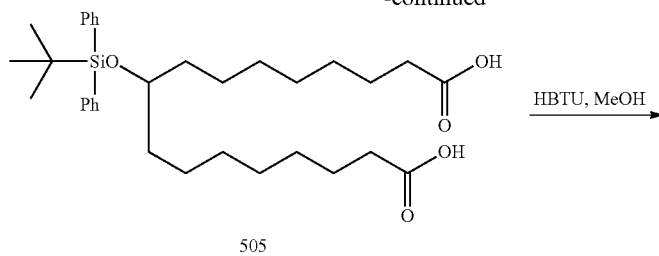


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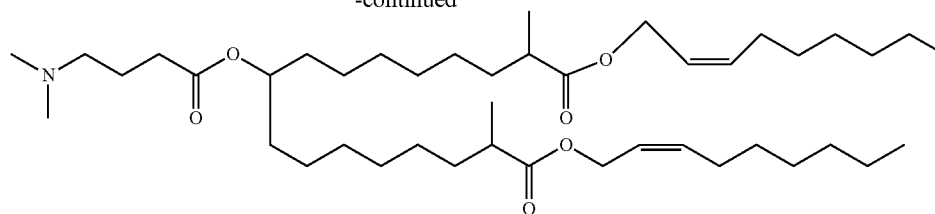


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167 mg, 66% (2 steps)

Compound 504: To a stirred solution of alcohol 11 (4.01 g, 22.25 mmol), TBDPS-Cl (12.24 g, 44.5 mmol) and DMAP (0.54 g, 4.42 mmol) was added triethyl amine (8.99 g, 90 mmol) and stirred at room temper for 14 h. To the above solution was added imidazole (1.51 g, 22.25 mmol) and continued to stir for 14 h at room temperature. 20 mL of water was added and extracted with DCM followed by washing with 2N HCl, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-10% ethyl acetate in hexane) to yield compound 504 (7.38 g, 79%, R_f: 0.8, 5% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.66 (m, 4H), 7.43-7.33 (m, 6H), 5.86-5.76 (m, 2H), 5.02-4.91 (m, 4H), 3.73-3.67 (m, 1H), 2.04-1.99 (m, 4H), 1.42-1.08 (m, 24H), 1.05 (s, 9H).

Compound 505: To a stirred solution of diene 504 (7.38 g, 17.6 mmol) and RuCl₃ (0.18 g, 0.88 mmol) in 400 mL of DCM/CH₃CN(1:1) was added NaIO₄ (37.6 g, 176 mmol) dissolved in 400 mL of water drop wise around 5° C. over 30 min. and stirred at room temperature for 3 h. The organic layer was separated followed by washing with 3% Na₂S solution (100 mL), water (250 mL) brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product 505 (4 g, 42%, R_f: 0.3, 40% ethyl acetate in hexane), which was used for the next step without further purification.

Compound 506: To a stirred solution of the acid 505 (4 g, 7.22 mmol), HBTU (6.02 g, 15.88 mmol), HOBt (2.14 g, 15.88 mmol) and DMAP (88 mg, 0.72 mmol) in 75 mL of dry DCM was added 5 mL of methanol and stirred at room temperature for 14 h. 10 mL of water was added followed by extraction with DCM (3×50 mL), washing with saturated NaHCO₃, water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-30% ethyl acetate in hexane) to yield compound 506 (2 g, 47.6%, R_f: 0.3, 10% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.65 (m, 4H), 7.41-7.33 (m, 6H), 3.70-3.64 (m, 1H), 3.66 (s, 6H), 2.28 (t, J=7.2 Hz, 4H), 1.63-1.07 (m, 24H), 1.04 (s, 9H).

Compound 507: To a stirred solution of dimethyl ester 506 (1.0 g, 1.79 mmol) in dry THF (20 mL) were added KHMDS (0.752 g, 3.76 mmol) and methyl iodide (0.762 g, 5.37 mmol) at 0° C. and then brought to room temperature over 30 min. and stirred for 24 h. 10 mL of sat. NH₄Cl solution was added followed by extraction with ethyl acetate (3×50 mL), washing with water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product, which was purified by column chromatography (0-5% ethyl acetate in hexane) to obtain the product 507 (0.218 g, 20%, R_f: 0.8, 5% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.65 (m, 4H), 7.41-7.33 (m, 6H),

3.70-3.67 (m, 1H), 3.67 (s, 6H), 2.43-2.38 (m, 2H), 1.59-1.07 (m, 24H), 1.13 (d, J=7.2 Hz, 6H), 1.04 (s, 9H).

Compound 509: To a stirred solution of methyl ester 507 (0.4 g, 0.66 mmol) in 10 mL of MeOH/THF (1:1) was added LiOH (0.079 g, 3.27 mmol) in 1 mL of water and stirred at room temperature for 24 h. To the above solution was added KOH (0.183 g, 3.27 mmol) in 1 mL of water and stirred for another 2 days. 2 mL of sat. NH₄Cl solution was added followed by extraction with ethyl acetate (3×25 mL), washing with water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product 508 (0.45 g, R_f: 0.2, 10% ethyl acetate in hexane), which was used for the next step without further purification. To a stirred solution of the above di-acid 508 (0.45 g), cis-2-Nonen-1-ol (0.66 g, 4.6 mmol) and EDC.HCl (0.82 g, 4.6 mmol) in dry DCM (15 mL) was added DIEA (1.2 g, 9.24 mmol) and stirred at room temperature for 3 days. 10 mL of water was added followed by extraction with DCM followed by washing with 2N HCl, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-10% ethyl acetate in hexane) to yield compound 509 (0.3 g, 55%, R_f: 0.5, 3% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.65 (m, 4H), 7.42-7.33 (m, 6H), 5.67-5.6 (m, 2H), 5.55-5.49 (m, 2H), 4.615 (d, J=4 Hz, 4H), 3.71-3.65 (m, 1H), 2.44-2.35 (m, 2H), 2.10 (q, J=8.0 Hz, 4H), 1.64-1.07 (m, 40H), 1.13 (d, J=8.0 Hz, 6H), 1.04 (s, 9H), 0.86 (t, J=10 Hz, 6H).

Compound 511: To a stirred solution of silyl ether 509 (0.3 g, 0.36 mmol) in dry THF were added pyridine (1 mL) and HF.Pyr., (1 mL) drop wise and stirred at 45° C. for 48 h. The solvent was evaporated and used for the next step without purification.

To a stirred solution of the above crude alcohol 510, N,N-Dimethyl amino butyric acid (0.34 g, 2.04 mmol), EDC.HCl (0.39 g, 2.04 mmol) and DMAP (0.06 g, 0.51 mmol) in dry DCM (10 mL) was added DIEA (0.5 g, 3.88 mmol) and stirred at room temperature for 2 days. 10 mL of water was added followed by extraction with DCM (3×25 mL), washing with saturated NaHCO₃, water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-30% ethyl acetate in 1% TEA containing hexane) to yield compound 511 (0.167 g, 66%, R_f: 0.4, 10% MeOH in DCM). Molecular weight for C₄₃H₇₉NO₆ (M+H)⁺ Calc. 706.59, Found 706.5.

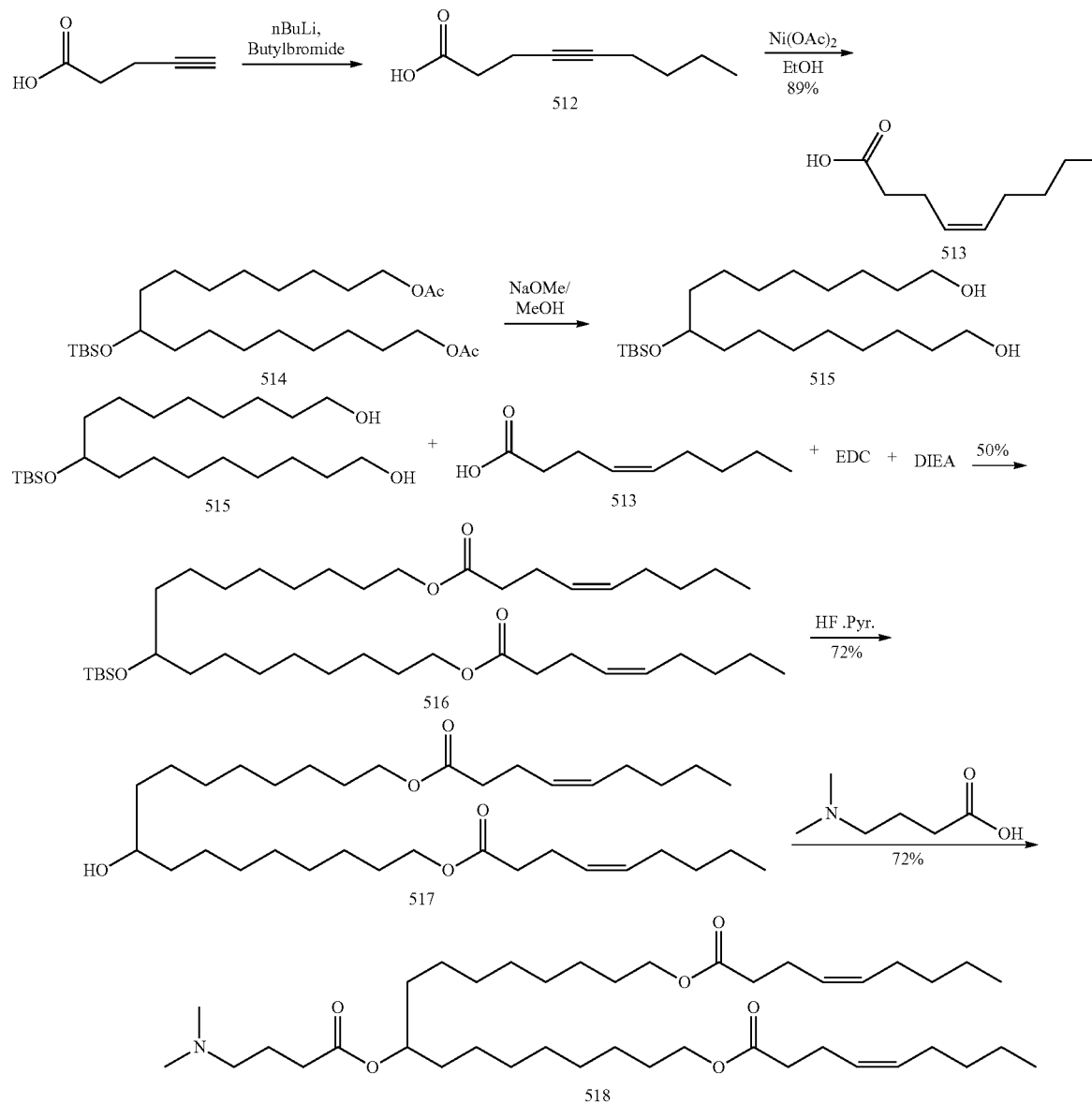
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Example 26

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Scheme 26



Compound 512: To a stirred solution of 4-Pentynoic acid in 100 mL of THF/HMPA (4:1) at -78°C . was added $n\text{BuLi}$ (3.1 g, 49 mmol) drop wise and stirred for 30 min. Then the reaction mixture was brought to 0°C . and stirred for 2 h. Again, the reaction mixture was cooled to -78°C . and n -butyl bromide (3.07 g, 22.44 mmol) was added drop wise and stirred at room temperature for 14 h. 10 mL of sat. NH_4Cl solution was added followed by extraction with ethyl acetate (3x25 mL), washing with water, brine and dried over anhydrous Na_2SO_4 . Concentration of the solvent gave the crude product, which was purified by column chromatography (0-30% ethyl acetate in hexane) to yield compound 512 (0.4 g, R_f : 0.8, 30% ethyl acetate in hexane). ^1H NMR (400 MHz, CDCl_3) δ 2.59-2.55 (m, 2H), 2.49-2.44 (m, 2H), 2.16-2.11 (m, 2H), 1.49-1.34 (m, 4H), 0.9 (t, $J=6.0$ Hz, 3H).

Compound 513: To a suspension of $\text{Ni}(\text{OAc})_2$ (0.45 g, 2.53 mmol) in EtOH (20 mL) was added NaBH_4 (0.096 g, 12.65 mmol) portion wise at room temperature and stirred for 15 min. under H_2 atm. Filtered off the solid followed by concentration of the solvent gave compound 513 (0.35 g, 88.6%, R_f : 0.6, 20% ethyl acetate in hexane). ^1H NMR (400 MHz, CDCl_3) δ 10.88 (br s, 1H), 5.47-5.41 (m, 1H), 5.35-5.31 (m, 1H), 2.43-2.33 (m, 4H), 2.07-2.03 (m, 2H), 1.36-2.27 (m, 4H), 0.9 (t, $J=8.0$ Hz, 3H).

Compound 515: To a stirred solution of di-acetate 514 (1.5 g, 3.09 mmol) in MeOH (100 mL) was added a piece of sodium metal (0.05 g, 2.17 mmol) and stirred at room temperature for 14 h. Neutralized with dry ice and concentrated followed by extraction with ethyl acetate (3x50 mL), washing with water, dried over anhydrous Na_2SO_4 . Con-

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centration of the solvent gave the crude product 515 (1.1 g, 88.7%), which was used for the next step without purification.

Compound 516: To a stirred solution of the above diol 515 (0.4 g, 1 mmol), 513 (0.341 g, 2.19 mmol), DMAP (0.1 g, 0.82 mmol) and EDC.HCl (0.57 g, 2.98 mmol) in dry DCM (15 mL) was added DIEA (5.97 g, 6 mmol) and stirred at room temperature for 2 days. 10 mL of water was added followed by extraction with ethyl acetate followed by washing with 1N HCl, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-10% ethyl acetate in hexane) to yield compound 516 (0.335 g, 50%, R_f: 0.6, 5% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 5.45-5.38 (m, 2H), 5.36-5.29 (m, 2H), 4.06 (t, J=8 Hz, 4H), 3.63-3.58 (m, 1H), 2.39-2.31 (m, 8H), 2.07-2.02 (m, 4H), 1.65-1.57 (m, 4H), 1.4-1.28 (m, 32H), 0.9 (t, J=6.0 Hz, 6H), 0.88 (s, 9H), 0.03 (s, 6H).

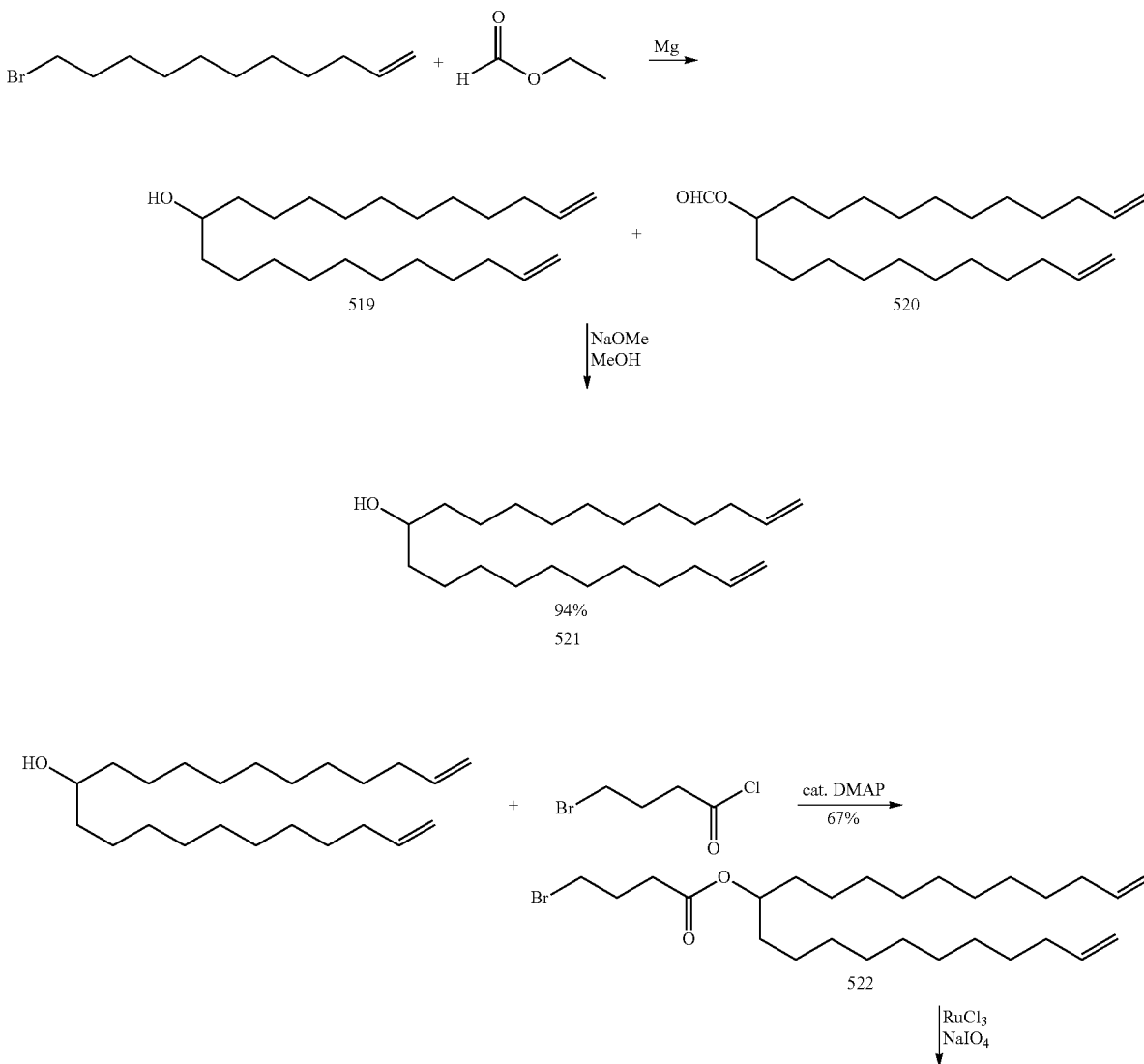
Compound 517: To a stirred solution of silyl ether 516 (0.3 g, 0.36 mmol) in dry THF (5 mL) were added pyridine (1 mL) and HF.Pyr. (1 mL) drop wise and stirred at 45° C. for 24 h. The solvent was evaporated followed by purification

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tion by column chromatography gave product 517 (0.2 g, 72%, R_f: 0.4, 10% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 5.43-5.36 (m, 2H), 5.34-5.27 (m, 2H), 4.04 (t, J=8 Hz, 4H), 3.59-3.53 (m, 1H), 2.37-2.3 (m, 8H), 2.05-2.0 (m, 4H), 1.61-1.29 (m, 37H), 0.88 (t, J=8.0 Hz, 6H).

Compound 518: To a stirred solution of the alcohol 517 (0.2 g, 0.355 mmol), N,N-Dimethyl amino butyric acid (0.36 g, 2.14 mmol), EDC.HCl (0.406 g, 2.14 mmol) and DMAP (0.043 g, 0.36 mmol) in dry DCM (10 mL) was added DIEA (0.55 g, 4.26 mmol) and stirred at room temperature for 2 days. 10 mL of water was added followed by extraction with DCM (3x25 mL), washing with saturated NaHCO₃, water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-30% ethyl acetate in 1% TEA containing hexane) to yield compound 518 (0.172 g, 72%, R_f: 0.2, 5% MeOH in DCM). ¹H NMR (400 MHz, CDCl₃) δ 5.43-5.36 (m, 2H), 5.32-5.27 (m, 2H), 4.87-4.83 (m, 1H), 4.03 (t, J=6 Hz, 4H), 2.36-2.2 (m, 6H), 2.32 (s, 6H), 2.03-1.25 (m, 40H), 0.88 (t, J=6.0 Hz, 6H).

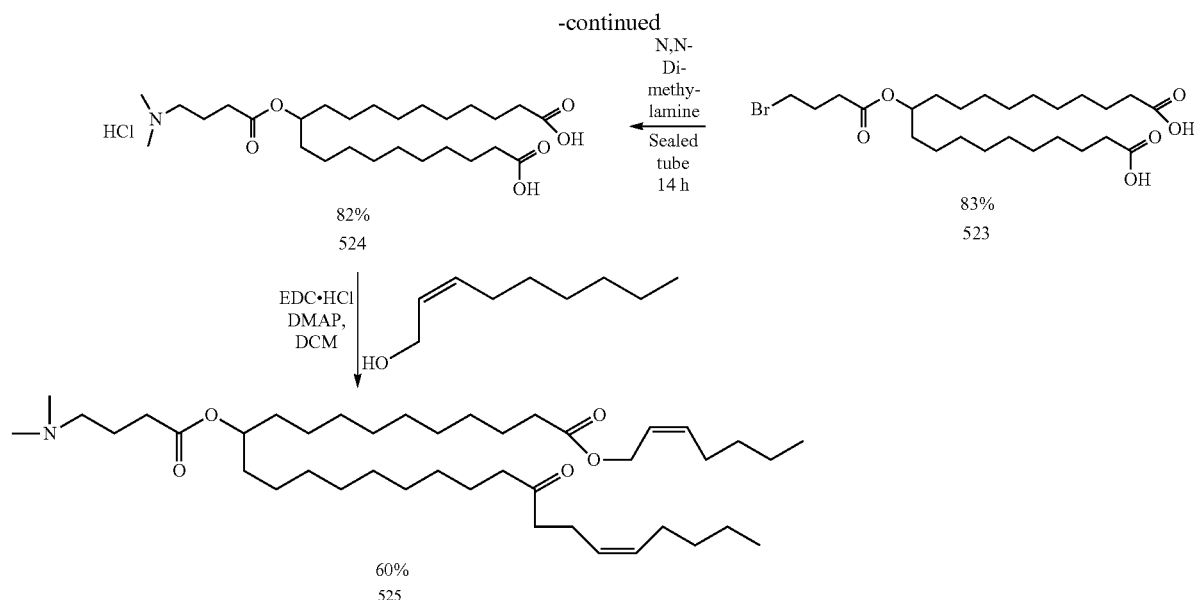
Example 27



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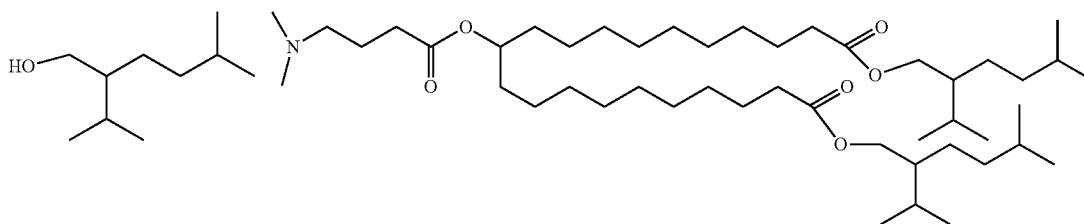
Compound 521: To a suspension of Mg in Et₂O was added alkyl bromide (25 g, 107.7 mmol) drop wise at 40° C. over one hour. Ethyl formate was added to the above reaction mixture at 0-5° C. and then the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was poured onto the ice cold sat. NH₄Cl solution followed by extraction with Et₂O (3×250 mL), washing with water, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product, which was re-dissolved in MeOH (250 mL) and a small piece of sodium (0.1 g) was added and stirred at room temperature for 14 h. The solvent was evaporated and 100 mL of water was added followed by filtration of the solid, washing with water (2×100 mL) gave pale yellow powder 521 (17 g, 94%, %, R_f: 0.8, 10% ethyl acetate in hexane). ¹H NMR (400 MHz, CDCl₃) δ 5.84-5.74 (m, 2H), 5.0-4.89 (m, 4H), 3.64-3.49 (m, 1H), 2.04-1.99 (m, 4H), 1.79 (br s, 1H), 1.44-1.23 (m, 32H).

Compound 522: To a stirred solution of 521 (10 g, 29.73 mmol) and DMAP (0.1 g, 0.82 mmol) in dry DCM (50 mL) was added 4-bromo butyryl chloride (6.56 g, 35.68 mmol)

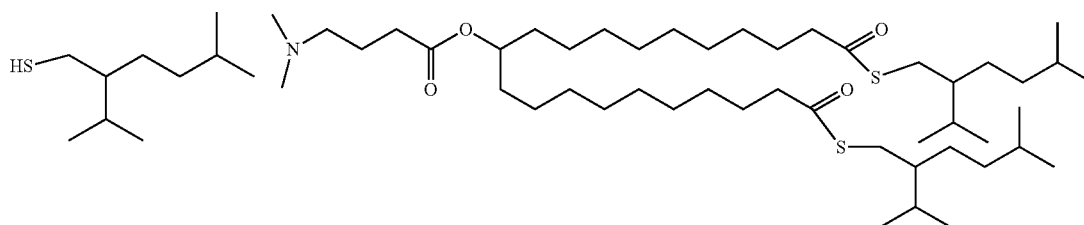
and stirred at room temperature for 14 h. 5 mL of saturated NaHCO₃ was added and the organic layer was separated and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product which was purified by column chromatography (0-10% ethyl acetate in hexane) to yield compound 522 (9.6 g, 66.7%, R_f: 0.9, 5% ethyl acetate in hexane).

Compound 524: Oxidation was carried out to get compound 523 (8.6 g, 83.5%, R_f: 0.1, 5% MeOH in DCM) following same experimental procedure as for compound 505. This crude material was dissolved in 2N N,N-dimethyl amine in THF (20 mL) and heated to 60° C. in a sealed tube for 14 h. Concentrated the reaction mixture and then pH of the reaction mixture was brought to 3. This mixture was freeze-dried to obtain compound 524 as HCl salt (4 g, 82%). Molecular weight for C₂₇H₅₁NO₆ (M+H)⁺ Calc. 486.37, Found 486.2. ¹H NMR (400 MHz, CDCl₃) δ 4.94-4.89 (m, 1H), 3.32-3.3 (m, 2H), 3.2-3.16 (m, 2H), 2.91 (s, 6H), 2.47 (t, J=8 Hz, 2H), 2.28 (t, J=8 Hz, 4H), 2.05-1.97 (m, 2H), 1.61-1.56 (8H), 1.4-1.25 (m, 22H).

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526s

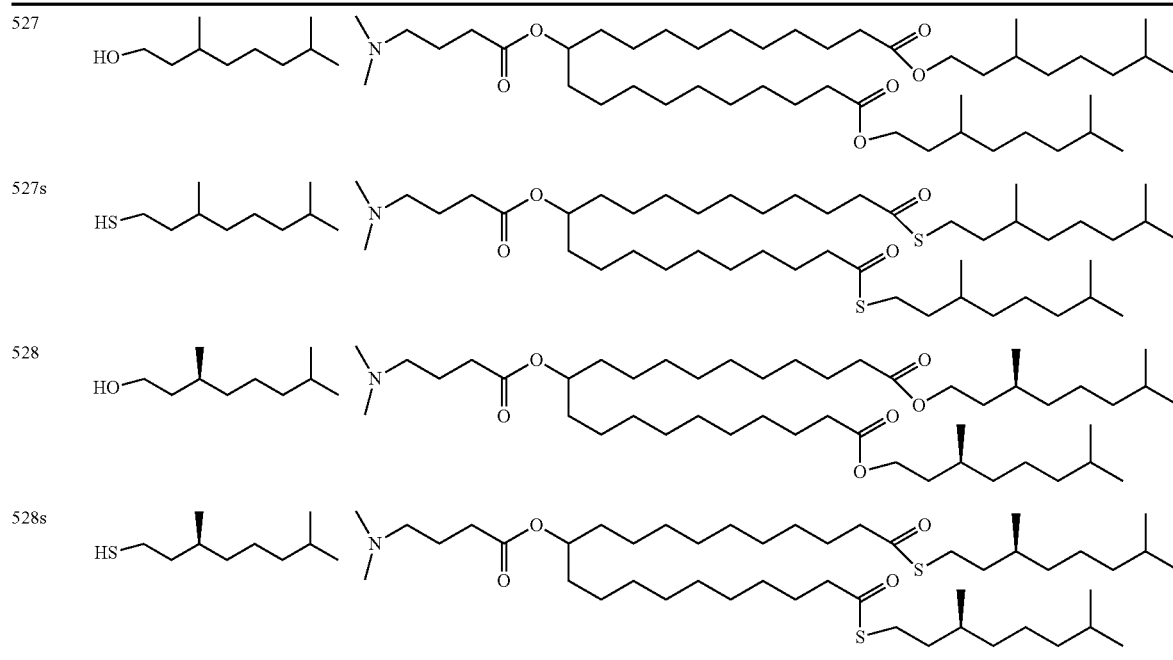


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-continued



Synthesis of Ester 525, 526, 527 and 528

The title compounds were synthesized following the experimental procedure as for compound 516.

Compound 525: (0.75 g, 60%, R_f : 0.3, 5% MeOH in DCM). ^1H NMR (400 MHz, CDCl_3) δ 5.65-5.59 (m, 2H), 5.53-5.47 (m, 2H), 4.87-4.81 (m, 1H), 4.595 (d, $J=4.0$ Hz, 4H), 2.43-2.25 (m, 8H), 2.2 (s, 6H), 2.1-2.03 (m, 4H), 1.81-1.73 (m, 2H), 1.61-1.56 (m, 4H), 1.48-1.47 (m, 4H), 1.36-1.23 (m, 32H), 0.86 (t, $J=8.0$ Hz, 6H).

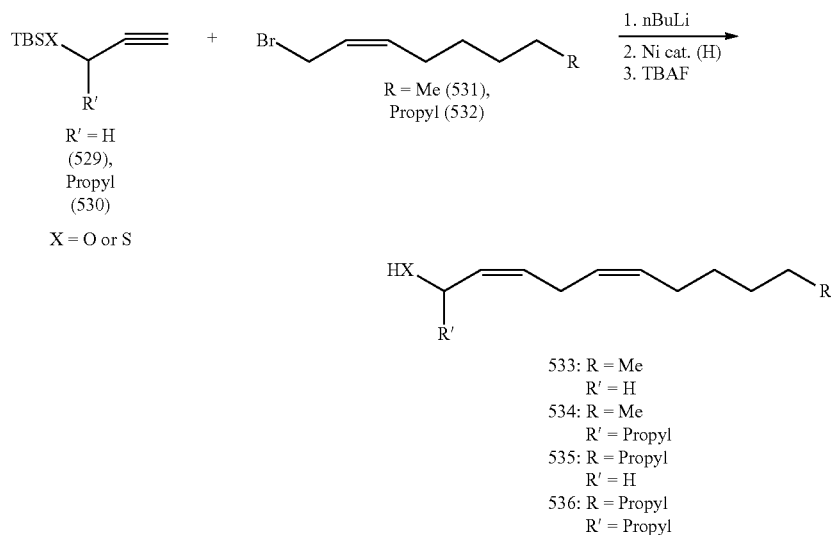
Compound 526: (0.358 g, 60.9%, R_f : 0.5, 5% MeOH in DCM). ^1H NMR (400 MHz, CDCl_3) δ 4.87-4.81 (m, 1H), 4.07-3.95 (m, 4H), 2.32-2.24 (m, 6H), 2.2 (s, 6H), 1.80-1.69 (m, 4H), 1.6-1.14 (m, 46H), 0.88-0.84 (m, 24H).

Compound 527: (0.258 g, 56.8%, R_f : 0.5, 5% MeOH in DCM). Molecular weight for $\text{C}_{47}\text{H}_{91}\text{NO}_6$ ($\text{M}+\text{H}$) $^+$ Calc. 766.23; Found: 766.7. ^1H NMR (400 MHz, CDCl_3) δ 4.86-4.80 (m, 1H), 4.12-4.02 (m, 4H), 2.31-2.23 (m, 8H), 2.19 (s, 6H), 1.80-1.72 (m, 2H), 1.66-1.06 (m, 52H), 0.87 (d, $J=8.0$ Hz, 6H), 0.84 (d, $J=8.0$ Hz, 12H).

Compound 528: (0.3 g, 68.1%, R_f : 0.5, 5% MeOH in DCM). Molecular weight for $\text{C}_{47}\text{H}_{91}\text{NO}_6$ ($\text{M}+\text{H}$) $^+$ Calc. 766.23; Found: 766.7. ^1H NMR (400 MHz, CDCl_3) δ 4.86-4.80 (m, 1H), 4.12-4.02 (m, 4H), 2.31-2.21 (m, 8H), 2.19 (s, 6H), 1.79-1.72 (m, 2H), 1.66-0.98 (m, 52H), 0.87 (d, $J=8.0$ Hz, 6H), 0.835 (d, $J=4.0$ Hz, 12H).

Example 28

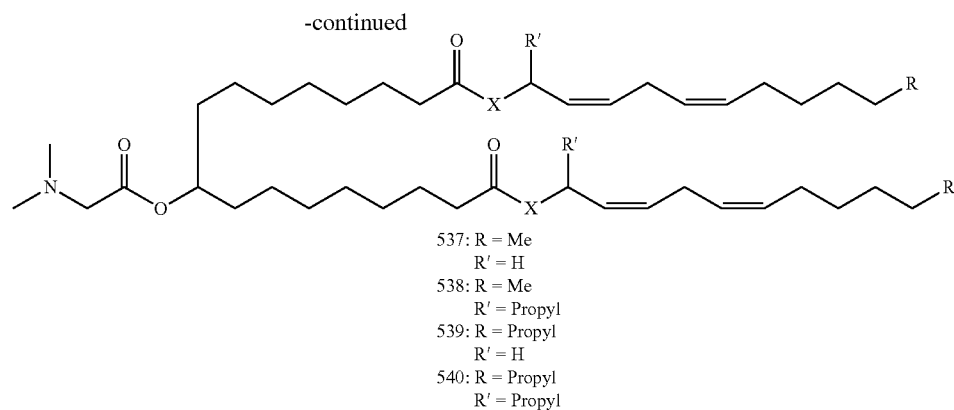
Scheme 28:



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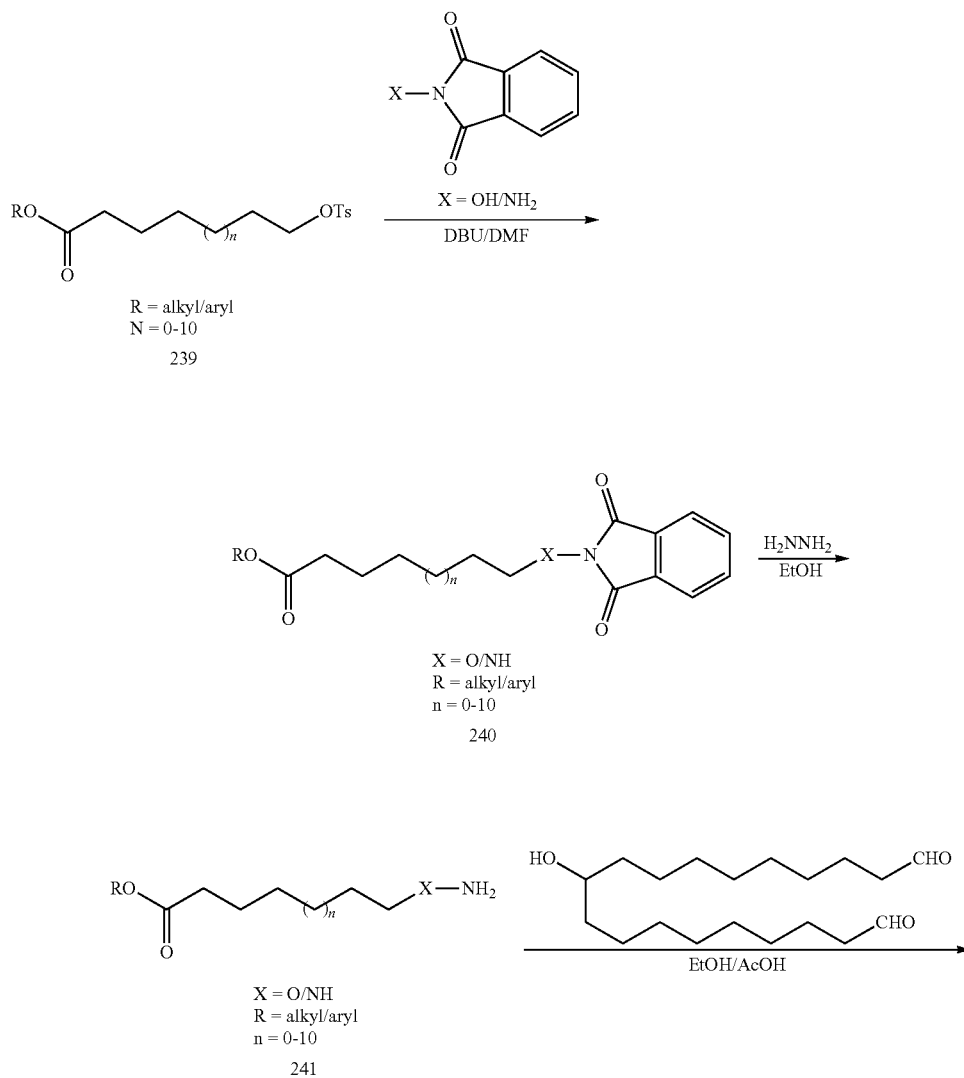


Synthesis of compounds 533, 534, 535 and 536: The title compounds (1 mmol) are synthesized following the experimental procedure of compound 513 except de-silylation step and it is done using TBAF in THF at room temperature.

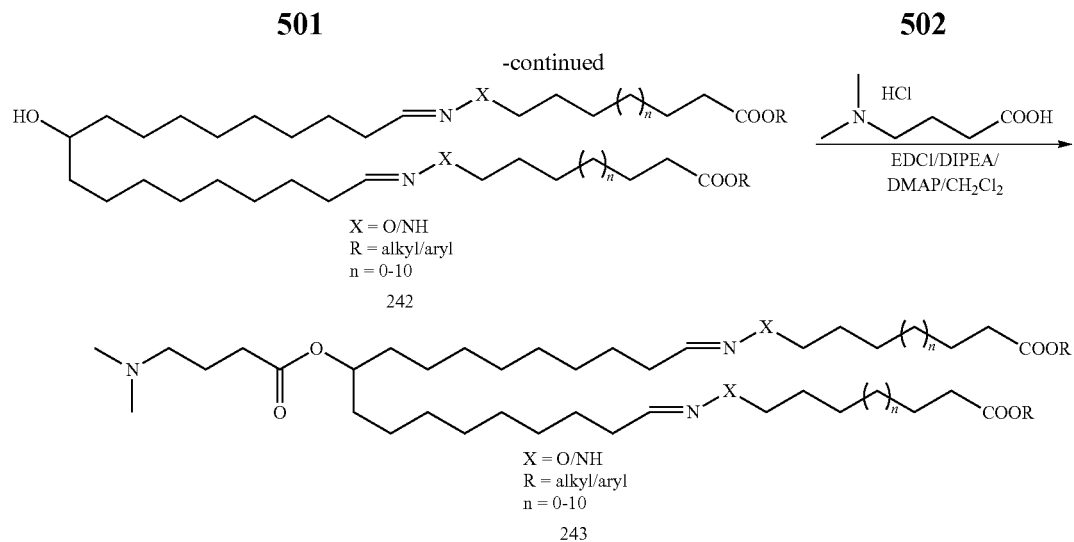
Synthesis of compounds 537, 538, 539 and 540: The title compounds (1 mmol) are synthesized following the experimental procedure of compound 525.

Example 29

Scheme 29

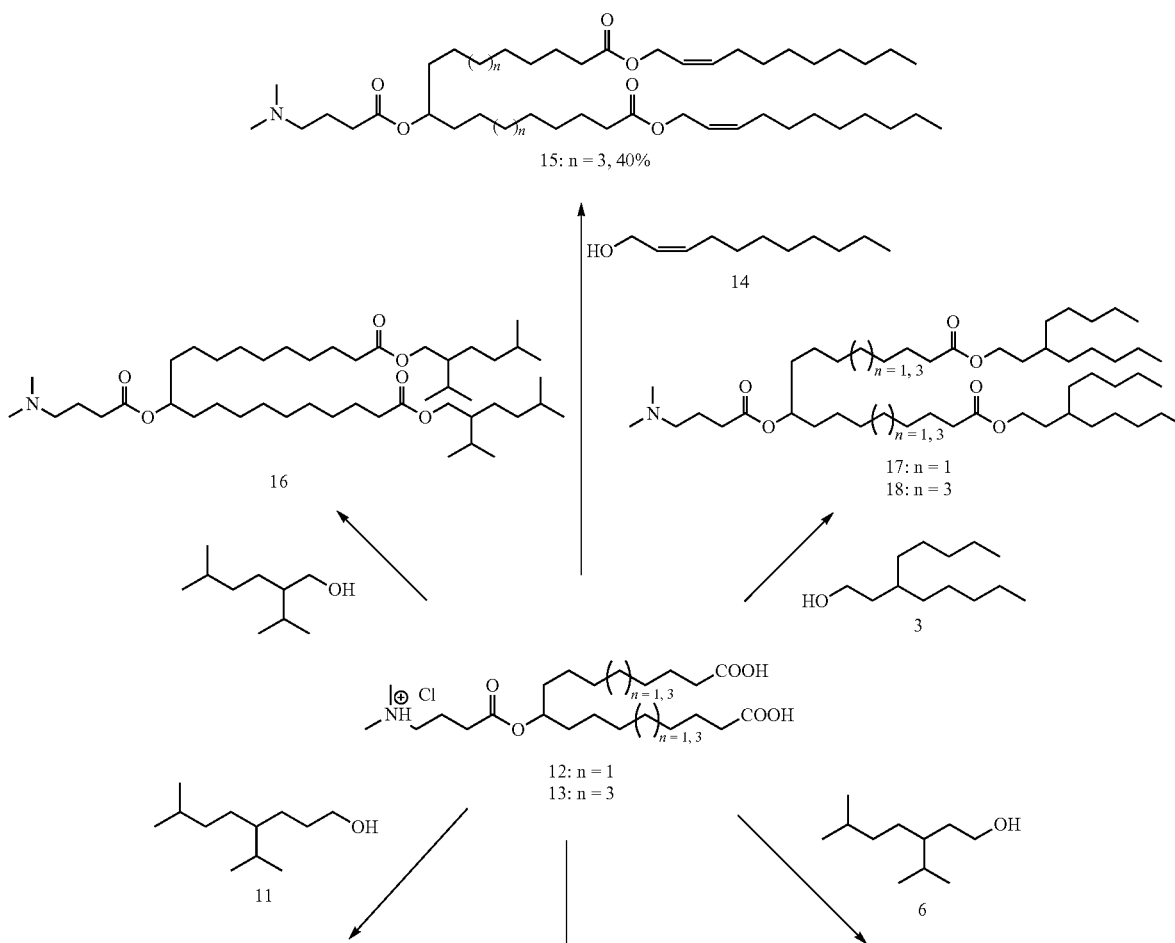


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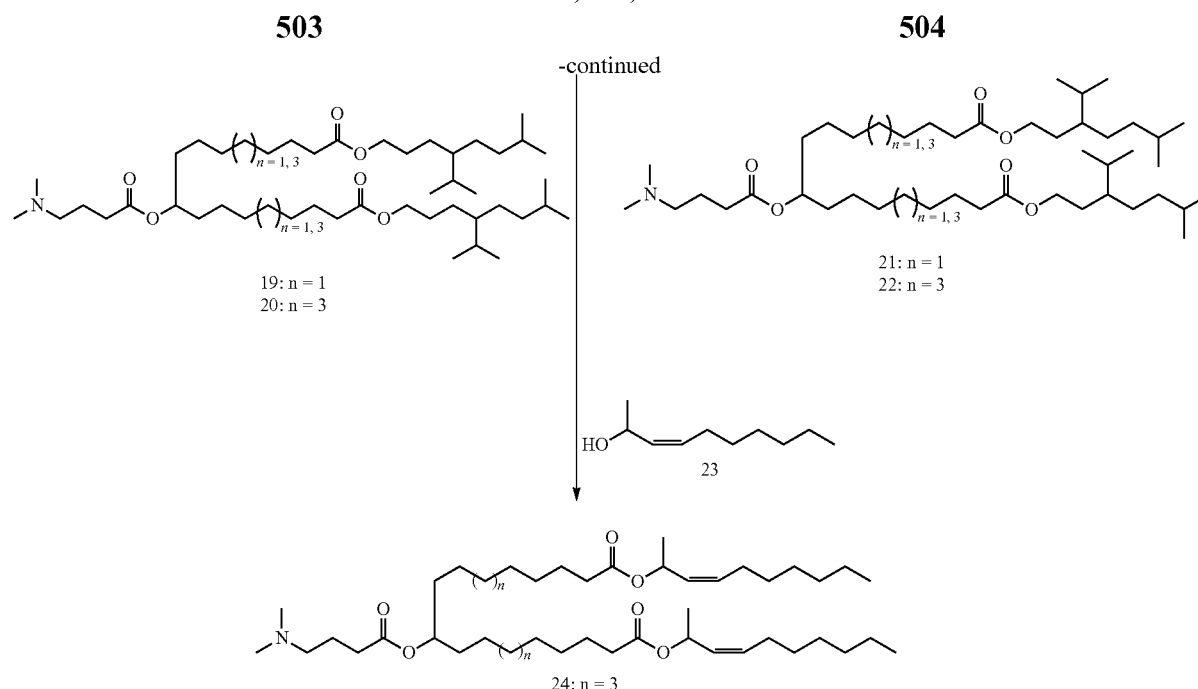


Compound 243 ($\text{X}=\text{O}/\text{NH}$, $\text{R}=\text{alkyl/aryl}$) can be synthesized as shown in Scheme 16-2. Tosyl group of 239 can be replaced with phthalimide group by nucleophilic substitution. After deprotection followed by coupling with 111 under acidic conditions, 242 can be synthesized. Standard esterification gives cationic lipid 243 and its analogs.

Example 30: Synthesis of Ester-Containing Lipids



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Compound 15: Compound 13 (503 mg, 1.0 mmol) was treated with 14 (469 mg, 3.0 mmol) in the presence of EDCI (2.30 g, 12.0 mmol), DMAP (235 mg, 1.92 mmol) and DIEA (8.34 mL, 47.9 mmol) in CH_2Cl_2 (50 mL) for 14 h. Aqueous work-up then column chromatography gave compound 15 (1.22 g, 1.54 mmol, 40%).

Molecular weight for $\text{C}_{49}\text{H}_{92}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 790.6925, Found 790.7.

Compound 16: This compound was synthesized from 13 and tetrahydrolavandulol using a procedure analogous to that described for compound 15. Yield: 0.358 g, 61%. ¹H NMR (400 MHz, CDCl_3) δ 4.87-4.81 (m, 1H), 4.07-3.95 (m, 4H), 2.32-2.24 (m, 6H), 2.2 (s, 6H), 1.80-1.69 (m, 4H), 1.6-1.14 (m, 46H), 0.88-0.84 (m, 24H).

Compound 17: This compound was synthesized from 12 (1.0 g, 2.15 mmol) and 3 (1.03 g, 5.16 mmol) using a procedure analogous to that described for compound 15.

Yield: 856 mg (50%). ¹H NMR (400 MHz, CDCl_3) δ 4.91-4.79 (m, 1H), 4.08 (t, J=7.1 Hz, 4H), 2.35-2.25 (m, 14H), 1.89-1.76 (m, 2H), 1.67-1.13 (m, 62H), 0.88 (t, J=7.0 Hz, 12H). ¹³C NMR (100 MHz, CDCl_3) δ 174.08, 74.45, 63.08, 45.27, 34.76, 34.56, 34.28, 33.70, 32.61, 32.39, 29.54, 29.36, 29.28, 26.36, 25.47, 25.13, 22.83, 14.26. Molecular weight for $\text{C}_{49}\text{H}_{96}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 794.7238, Found 794.6.

Compound 18: This compound was synthesized from 13 (1.0 g, 2.15 mmol) and 3 (1 g) using a procedure analogous to that described for compound 15.

Yield: 1 g (59%). ¹H NMR (400 MHz, CDCl_3) δ 4.94-4.74 (m, 1H), 4.17-3.85 (m, 4H), 2.46-2.19 (m, 12H), 1.93-1.79 (m, 2H), 1.74-1.45 (m, 10H), 1.37 (d, J=20.2 Hz, 2H), 1.35-1.13 (m, 44H), 0.88 (t, J=6.9 Hz, 12H). ¹³C NMR (101 MHz, CDCl_3) δ 174.19, 77.53, 77.21, 76.90, 63.12, 34.81, 34.66, 34.35, 33.76, 32.66, 32.45, 29.76, 29.73, 29.63, 29.48, 29.39, 26.42, 25.57, 25.23, 22.89, 14.32. Molecular weight for $\text{C}_{53}\text{H}_{103}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 850.38, Found 850.7.

Compound 19: This compound was synthesized from 12 and 11 using a procedure analogous to that described for compound 15.

Yield: 860 mg (51%). ¹H NMR (400 MHz, CDCl_3) δ 4.90-4.81 (m, 1H), 4.04 (t, J=6.8 Hz, 4H), 2.37-2.17 (m, 14H), 1.84-1.06 (m, 48H), 0.93-0.78 (m, 24H). ¹³C NMR (100 MHz, CDCl_3) δ 174.06, 74.35, 65.51, 64.91, 59.05, 45.51, 43.77, 37.10, 34.55, 34.29, 32.55, 29.54, 29.37, 29.34, 29.28, 28.58, 28.19, 26.99, 26.74, 25.47, 25.15, 22.90, 22.82, 19.60, 19.41, 19.28. Molecular weight for $\text{C}_{47}\text{H}_{92}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 766.6925, Found 766.5.

Compound 20: This compound was synthesized from 13 and 11 using a procedure analogous to that described for compound 15.

¹H NMR (400 MHz, CDCl_3) δ 4.86 (p, J=6.2 Hz, 1H), 4.04 (t, J=6.7 Hz, 4H), 2.38-2.17 (m, 14H), 1.84-1.07 (m, 56H), 0.93-0.76 (m, 24H). ¹³C NMR (100 MHz, CDCl_3) δ 174.11, 173.46, 74.44, 64.90, 59.06, 45.51, 43.77, 37.11, 34.59, 34.32, 32.57, 29.71, 29.67, 29.57, 29.43, 29.34, 28.58, 28.20, 27.00, 26.75, 25.51, 25.20, 22.90, 22.82, 19.41, 19.28. Molecular weight for $\text{C}_{51}\text{H}_{100}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 822.7551, Found 822.6.

Compound 21: This compound was synthesized from 12 and 6 using a procedure analogous to that described for compound 15.

¹H NMR (400 MHz, CDCl_3) δ 4.91-4.78 (m, 1H), 4.15-3.98 (m, 4H), 2.39-2.18 (m, 14H), 1.84-1.11 (m, 44H), 0.92-0.77 (m, 24H). ¹³C NMR (100 MHz, CDCl_3) δ 174.06, 173.44, 74.36, 63.73, 59.03, 45.48, 41.00, 36.98, 34.56, 34.29, 32.54, 29.60, 29.54, 29.49, 29.36, 29.28, 28.52, 25.47, 25.13, 23.15, 22.85, 22.81, 19.49, 18.89. Molecular weight for $\text{C}_{45}\text{H}_{88}\text{NO}_6$ ($\text{M}+\text{H}$)⁺ Calc. 738.6612, Found 738.6.

Compound 22: This compound was synthesized from 13 and 6 using a procedure analogous to that described for compound 15.

Yield: 900 mg (57%). ¹H NMR (400 MHz, CDCl_3) δ 4.92-4.78 (m, 1H), 4.15-3.91 (m, 4H), 3.33-3.08 (m, 1H), 2.36-2.15 (m, 14H), 1.79 (dq, J=14.3, 7.2 Hz, 2H), 1.74-1.55 (m, 8H), 1.55-1.37 (m, 9H), 1.35-0.95 (m, 36H), 0.96-0.61

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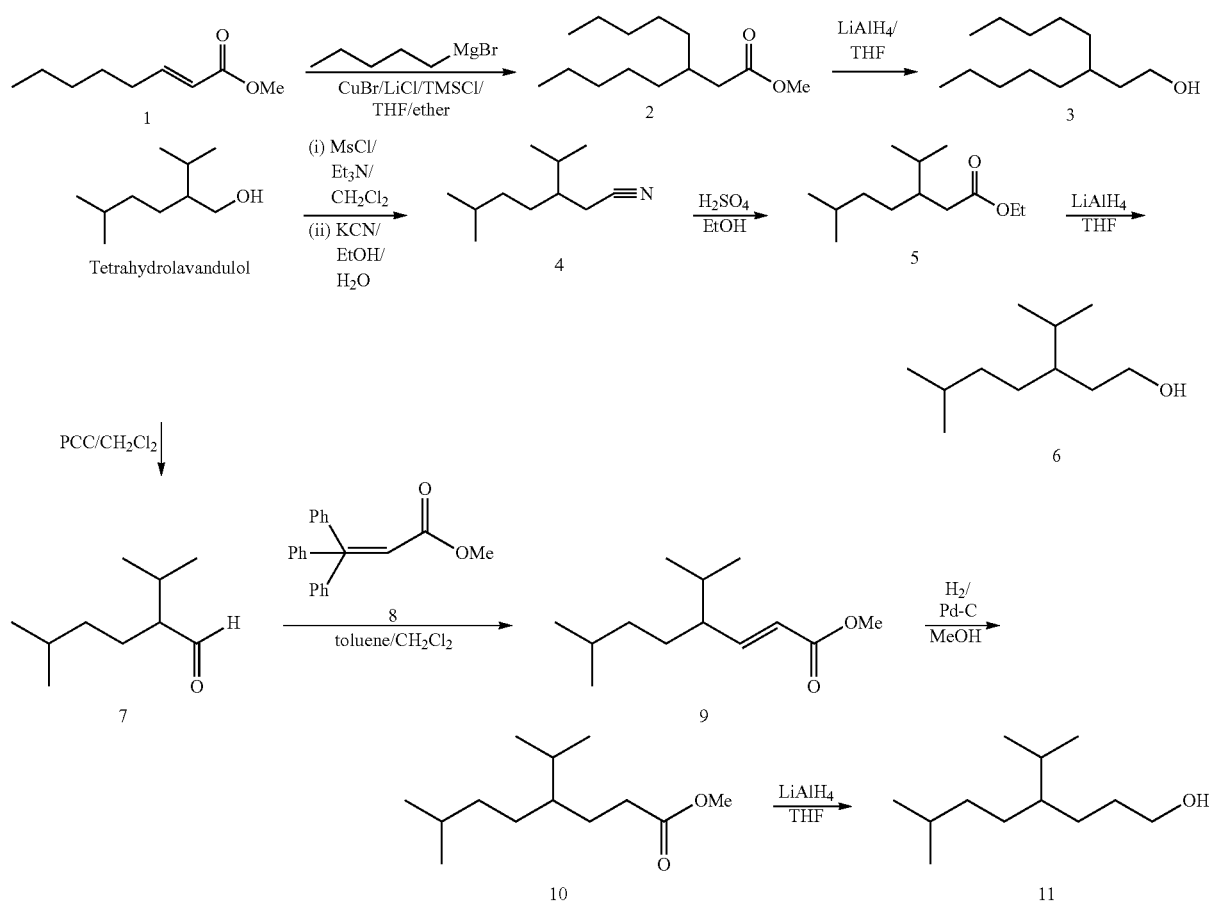
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(m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.16, 173.52, 77.54, 77.22, 76.91, 74.48, 63.76, 59.10, 45.55, 42.02, 41.04, 38.75, 37.09, 37.02, 34.65, 34.36, 32.62, 30.71, 29.75, 29.72, 29.64, 29.62, 29.53, 29.48, 29.44, 29.38, 28.56, 28.45, 25.56, 25.23, 23.59, 23.23, 22.90, 22.86, 19.54, 19.03, 18.94. Molecular weight for $\text{C}_{49}\text{H}_{95}\text{NO}_6$ (M+H) $^+$ Calc. 794.2817, Found 794.7.

Compound 24: This compound was synthesized from 13 and 23 using a procedure analogous to that described for compound 15.

Yield: 0.567 g (30%). ^1H NMR (400 MHz, CDCl_3) δ 4.85 (p, J=6.1 Hz, 1H), 4.20-3.93 (m, 4H), 2.41-2.18 (m, 13H), 1.92-1.72 (m, 2H), 1.56 (ddd, J=27.4, 16.4, 5.8 Hz, 12H), 1.39 (s, 2H), 1.25 (s, 54H), 0.91 (dt, J=13.7, 6.4 Hz, 11H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.18, 173.51, 77.54, 77.23, 76.91, 74.50, 63.12, 59.10, 45.55, 34.81, 34.66, 34.38, 33.76, 32.67, 32.62, 32.45, 29.77, 29.73, 29.64, 29.49, 29.39, 26.42, 25.57, 25.24, 23.23, 22.89, 14.32. Molecular weight for $\text{C}_{47}\text{H}_{88}\text{NO}_6$ (M+H) $^+$ Calc. 762.6612, Found 762.5.

Example 31: Synthesis of Alcohol Components



Compound 2: Compound 2 was synthesized from 1 using a procedure analogous to that described in *Journal of the Organic Chemistry*, 2009, 1473.

^1H NMR (400 MHz, CDCl_3) δ 3.66 (s, 3H), 2.23 (d, J=6.9 Hz, 2H), 1.84 (brs, 1H), 1.27 (d, J=11.5 Hz, 16H), 0.88 (t, J=6.8 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.29, 51.49, 39.25, 35.22, 34.00, 32.24, 26.34, 22.77, 14.22.

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Compound 3: To a suspension of LiAlH_4 (2.84 g, 74.9 mmol) in THF (85 mL) was added a solution of compound 2 (8.55 g, 37.4 mmol) in THF (25 mL). The reaction mixture was refluxed overnight. Aqueous workup then column chromatography gave pure compound 3 (7.35 g, 36.7 mmol, 98%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.66 (t, J=7.0 Hz, 2H), 1.59-1.12 (m, 19H), 0.88 (t, J=6.9 Hz, 6H).

Compound 4: Tetrahydrolavandulol (10.1 g, 63.8 mmol) was treated with methanesulfonyl chloride (6.38 mL) in CH_2Cl_2 (200 mL) and Et_3N (17.6 mL). Aqueous workup gave the crude mesylate, which was treated with KCN (4.98 g, 76.5 mmol) in EtOH (90 mL) and H_2O (10 mL). Aqueous workup then column chromatography gave pure compound 4 (8.36 g, 50.0 mmol, 72%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 2.38-2.23 (m, 2H), 1.86-1.78 (m, 1H), 1.59-1.42 (m, 3H), 1.40-1.07 (m, 3H), 0.93-0.89 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ 119.73, 41.69, 36.46, 30.10, 28.44, 28.33, 22.82, 22.59, 19.62, 19.11, 19.05.

Compound 6: The cyano derivative 4 was converted to the ethyl ester under acidic conditions to give compound 5 and the ester was reduced by LiAlH_4 in THF to give compound 6.

Compound 7: Tetrahydrolavandulol (98.1 g, 51.2 mmol) was oxidized with PCC (16.6 g, 76.8 mmol) in CH_2Cl_2 (200

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mL). Aqueous workup then column chromatography gave pure compound 7 (6.19 g, 39.6 mmol, 77%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 9.60 (d, J=3.1 Hz, 1H), 2.05-1.79 (m, 1H), 1.71-1.36 (m, 4H), 1.23-1.04 (m, 2H), 1.02-0.82 (m, 12H).

Compound 9: To a solution of compound 7 (2.0 g, 12.8 mmol) in toluene (40 mL) and CH₂Cl₂ (18 mL) and was added 8 (3.96 g, 11.8 mmol). The mixture was heated at 70° C. overnight. Column chromatography gave pure compound 9 (1.40 g, 6.59 mmol, 51%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 6.77 (dd, J=15.6, 9.9 Hz, 1H), 5.76 (d, J=15.6 Hz, 1H), 3.73 (s, 3H), 1.97-1.83 (m, 1H), 1.72-1.64 (m, 1H), 1.54-1.40 (m, 2H), 1.37-1.22 (m, 1H), 1.18-0.97 (m, 2H), 0.94-0.78 (m, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 167.19, 152.54, 121.70, 51.53, 49.66, 36.95, 31.76, 29.49, 28.29, 22.92, 22.54, 20.84, 19.24.

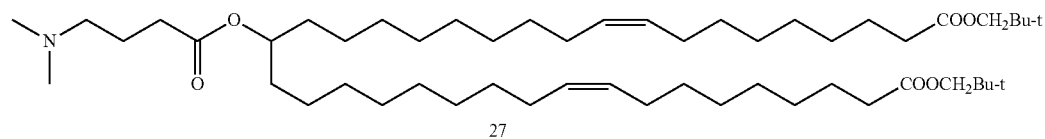
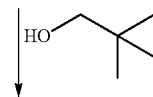
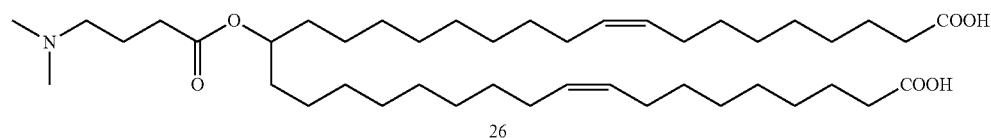
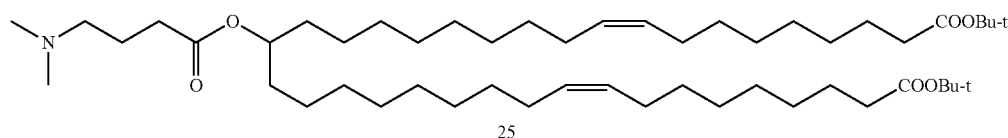
Compound 10: To a solution of compound 9 (1.0 g, 4.71 mmol) in MeOH (15 mL) was added Pd—C (125 mg). The mixture was stirred under H₂ atmosphere overnight. The mixture was filtered over Celite then evaporated to give pure compound 10 (924 mg, 4.31 mmol, 92%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 3H), 2.41-2.16 (m, 2H), 1.74-1.57 (m, 2H), 1.57-1.42 (m, 2H), 1.33-1.02 (m, 5H), 0.88-0.83 (m, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 174.78, 51.62, 43.71, 36.97, 32.69, 29.23, 28.56, 27.94, 25.92, 22.85, 22.79, 19.32, 19.19.

Compound 11: To a suspension of LiAlH₄ (444 mg, 11.7 mmol) in THF (12 mL) was added a solution of compound 10 (1.25 g, 5.83 mmol) in THF (8 mL). The reaction mixture was refluxed overnight. Aqueous workup gave the crude compound 11 (1.1 g) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 3.63 (t, J=6.7 Hz, 2H), 1.74-1.66 (m, 1H), 1.60-1.45 (m, 3H), 1.37-1.05 (m, 7H), 0.88-0.82 (m, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 63.75, 44.00, 37.16, 31.22, 29.40, 28.61, 28.28, 26.62, 22.90, 22.82, 19.43, 19.28.

Example 32: Synthesis of Ester-Containing Lipids



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Compound 26: Compound 25 (840 mg, 1.03 mmol) was stirred in TFA (9 mL) and CH₂Cl₂ (36 mL) for 3 h at room temperature. Evaporation of the solvents and co-evaporation with toluene 3 times gave compound 26.

Molecular weight for C₄₃H₈₀NO₆ (M+H)⁺ Calc. 706.5986, Found 706.4.

Compound 27: Compound 26 from the previous step was treated with 2,2-dimethylpropanol (363 mg, 4.12 mmol) in the presence of EDCI (592 mg, 3.09 mmol), DMAP (50 mg, 0.412 mmol) and DIEA (1.44 mL, 8.24 mmol) in CH₂Cl₂ (10 mL) for 14 h. Aqueous work-up then column chromatography gave compound 27 (575 mg, 0.679 mmol, 66%).

¹H NMR (400 MHz, CDCl₃) δ 5.40-5.28 (m, 4H), 4.91-4.81 (m, 1H), 3.76 (s, 4H), 2.34-2.27 (m, 8H), 2.22 (s, 6H), 2.03-1.97 (m, 8H), 1.83-1.26 (m, 50H), 0.94 (s, 18H). ¹³C NMR (100 MHz, CDCl₃) δ 174.14, 173.53, 130.09, 129.92, 74.41, 73.72, 59.12, 45.61, 34.60, 34.32, 32.64, 31.45, 29.93, 29.85, 29.71, 29.68, 29.48, 29.32, 29.28, 27.39, 27.33, 26.62, 25.52, 25.22, 23.32.

Molecular weight for C₅₃H₁₀₀NO₆ (M+H)⁺ Calc. 846.7551, Found 846.5.

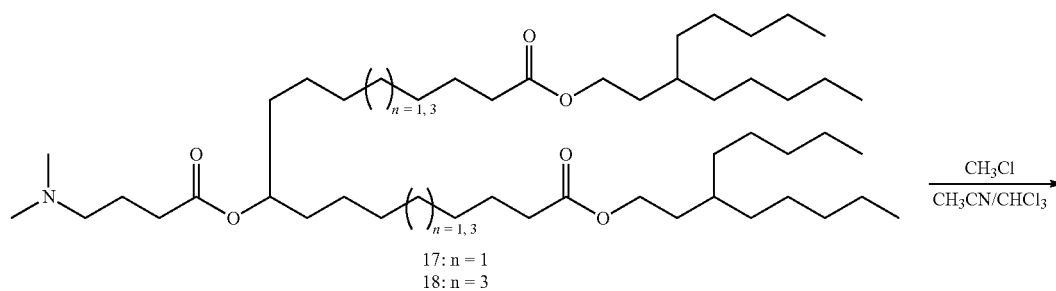
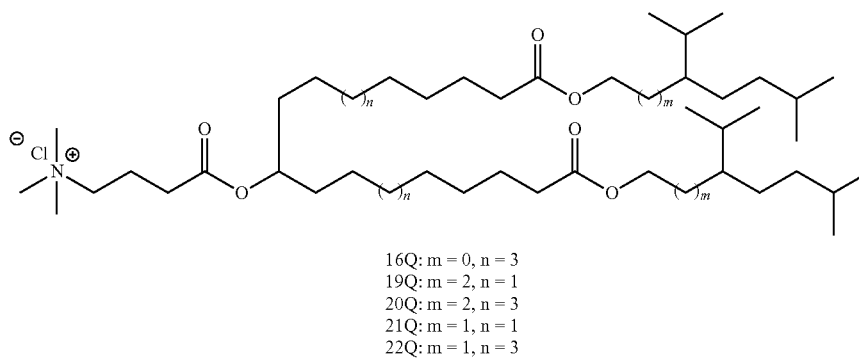
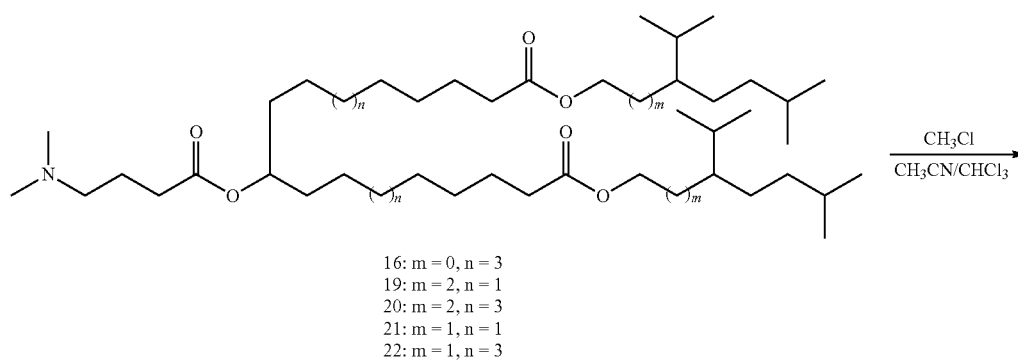
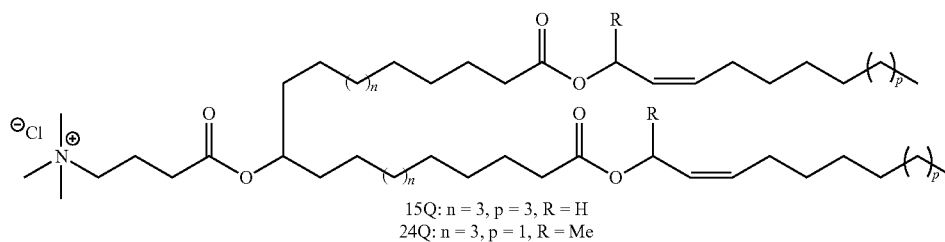
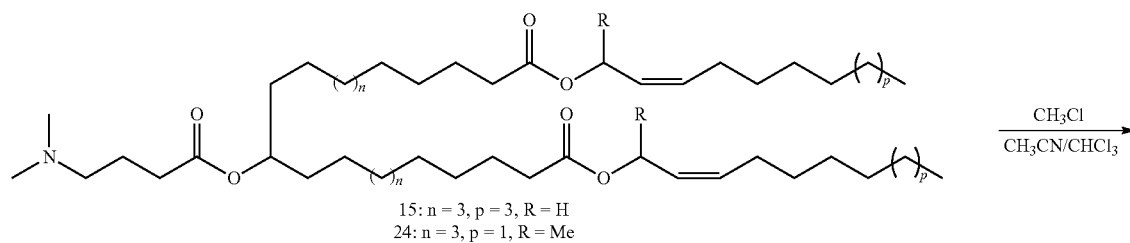
Example 33: Synthesis of Quaternary Lipids

A. The amino lipids synthesized in Examples 31 and 32 can be converted to the corresponding quaternary lipids as shown below by treatment with CH₃Cl in CH₃CN and CHCl₃.

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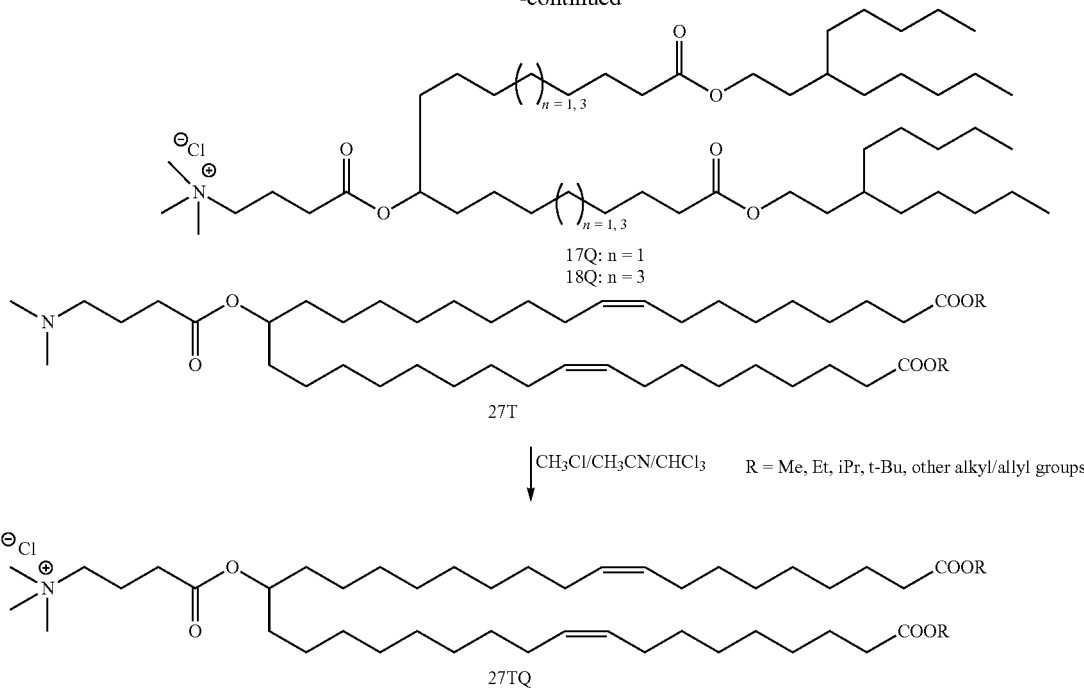


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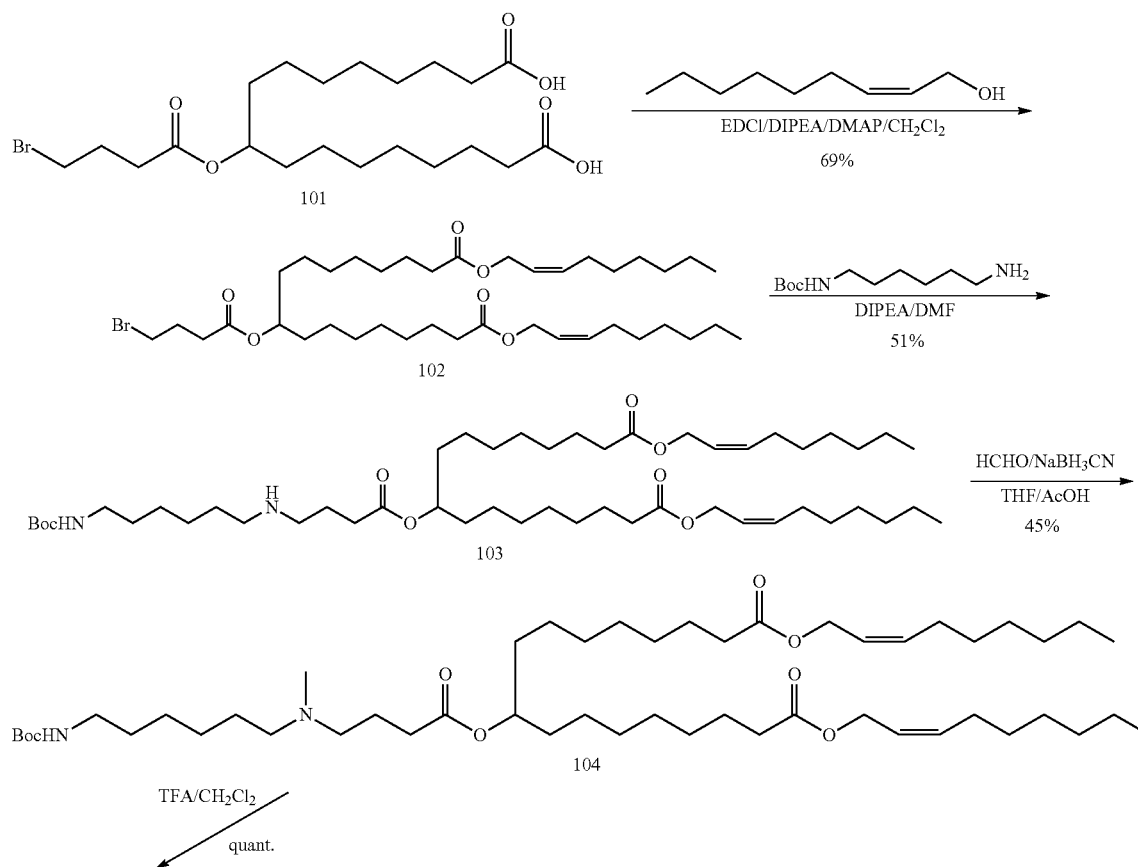
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B. Synthesis of BODIPY-Lipid Conjugates

Synthesis of BODIPY-labeled lipid

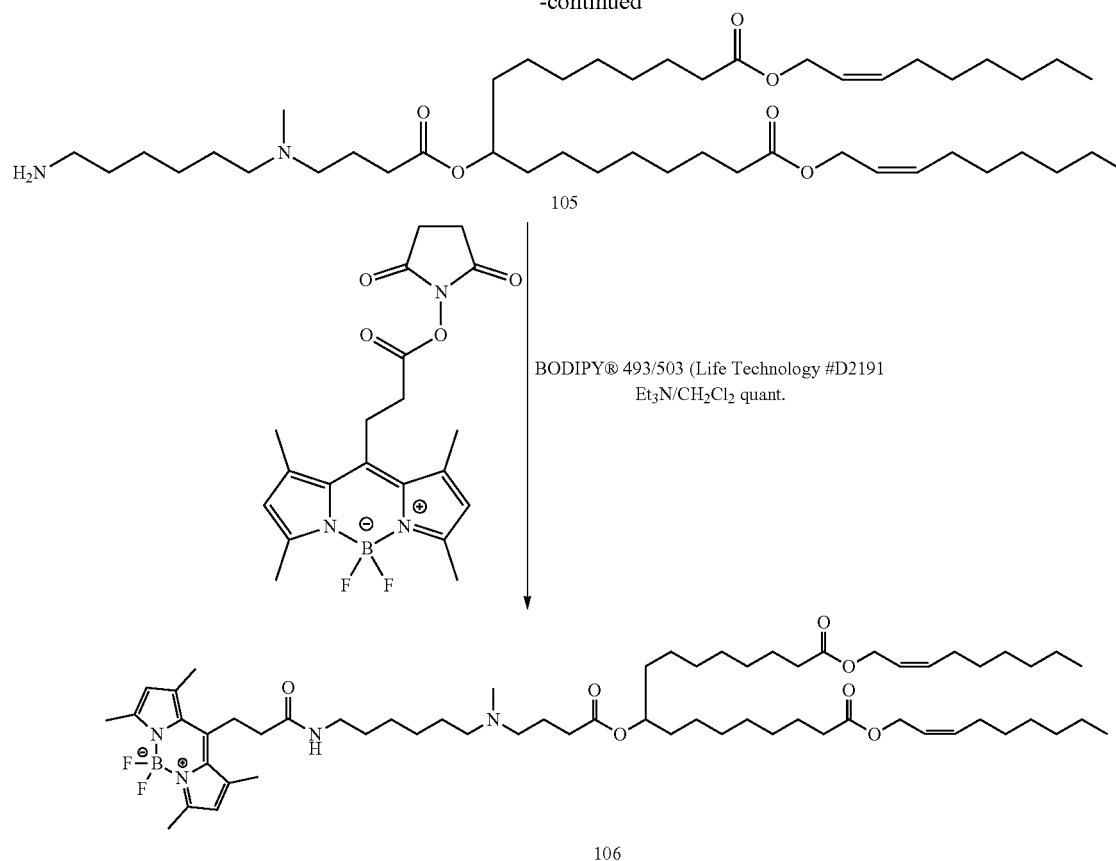


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Compound 102: To a solution of compound 101 (2.00 g, 4.30 mmol) and cis-2-nonen-1-ol (1.81 mL, 10.7 mmol) in CH₂Cl₂ (20 mL) were added diisopropylethylamine (3.00 mL, 17.2 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.06 g, 10.7 mmol) and DMAP (106 mg, 0.868 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with CH₂Cl₂ (200 mL) and washed with saturated NaHCO₃ aq. (100 mL). The organic layer was dried over MgSO₄, filtered and concentrated. The crude was purified by silica gel column chromatography (0-5% EtOAc in Hexane) to give compound 102 (2.11 g, 2.96 mmol, 69%, R_f=0.45 developed with 10% EtOAc in Hexane).

¹H NMR (500 MHz, CDCl₃) δ 5.67-5.61 (m, 2H), 5.54-5.49 (m, 2H), 4.89-4.84 (m, 1H), 4.62 (d, J=6.5 Hz, 4H), 3.46 (t, J=6.5 Hz, 2H), 2.48 (t, J=7.3 Hz, 2H), 2.30 (t, J=7.5 Hz, 4H), 2.20-2.14 (m, 2H), 2.12-2.04 (m, 4H), 1.63-1.60 (m, 4H), 1.51-1.50 (m, 4H), 1.37-1.27 (m, 32H), 0.88 (t, J=6.8 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 173.90, 172.45, 135.58, 123.51, 74.74, 60.36, 34.47, 34.24, 32.93, 32.91, 31.83, 29.54, 29.48, 29.31, 29.21, 29.01, 28.03, 27.70, 25.43, 25.08, 22.76, 14.23.

Molecular weight for C₃₉H₆₉BrNaO₆ (M+Na)⁺ Calc. 735.42, Found 735.2.

Compound 103: To a solution of 102 (2.11 g, 2.96 mmol) in DMF (20 mL) was added a solution of N-Boc-1,6-diaminohexane (670 mg, 3.10 mmol) in DMF (20 mL) at 0° C. The mixture was stirred for 18 hours at room temperature. Then additional N-Boc-1,6-diaminohexane (160 mg, 0.740 mmol) in DMF (1 mL) was added and the mixture was stirred for 12 hour. The reaction was quenched by adding

saturated NaHCO₃ aq. (100 mL) then extracted with Et₂O (150 mL×3). The organic layer was separated and dried over anhydrous MgSO₄. After filtration and concentration, the crude was purified by silica gel column chromatography (5% MeOH in CH₂Cl₂, R_f=0.24) to give 103 (1.28 g, 1.51 mmol, 51%).

¹H NMR (400 MHz, CDCl₃) δ 5.67-5.61 (m, 2H), 5.55-5.50 (m, 2H), 4.88-4.81 (m, 1H), 4.61 (d, J=6.8 Hz, 4H), 4.54 (brs, 1H), 3.11-3.08 (m, 2H), 2.67-2.59 (m, 4H), 2.35 (t, J=7.4 Hz, 2H), 2.29 (t, J=7.6 Hz, 4H), 2.10-2.07 (m, 4H), 1.84-1.81 (m, 4H), 1.63-1.57 (m, 4H), 1.50-1.47 (m, 8H), 1.44 (s, 9H), 1.38-1.27 (m, 34H), 0.88 (t, J=6.8 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 173.90, 173.53, 135.57, 123.50, 74.49, 60.36, 49.82, 49.29, 40.64, 34.47, 34.24, 32.68, 31.83, 30.16, 29.89, 29.54, 29.50, 29.33, 29.23, 29.01, 28.58, 27.69, 27.11, 26.80, 25.44, 25.37, 25.09, 22.76, 14.23.

Molecular weight for C₅₀H₉₃N₂O₈ (M+H)⁺ Calc. 849.69, Found 849.5.

Compound 104: To a solution of 103 (1.16 g, 1.37 mmol) in THF (20 mL) were added formaldehyde (37 wt. % in H₂O, 0.306 mL, 4.11 mmol), sodium cyanoborohydride (1 M solution in THF, 2.06 mL, 2.06 mmol) and acetic acid (0.008 mL, 0.137 mmol) at 0° C. The mixture was stirred at room temperature for 17 hours. The reaction was quenched by adding saturated NaHCO₃ aq. (50 mL) then extracted with Et₂O (100 mL×3). The organic layer was separated and dried over anhydrous MgSO₄. After filtration and concentration, the crude was purified by silica gel column chromatography (8% MeOH in CH₂Cl₂, R_f=0.46) to give 104 (531 mg, 0.615 mmol, 45%).

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^1H NMR (400 MHz, CDCl_3) δ 5.66-5.60 (m, 2H), 5.53-5.47 (m, 2H), 4.86-4.80 (m, 1H), 4.61-4.59 (m, 5H), 3.12-3.07 (m, 2H), 2.89-2.78 (m, 4H), 2.62 (s, 3H), 2.40 (t, J=6.8 Hz, 2H), 2.28 (t, J=7.4 Hz, 4H), 2.11-2.06 (m, 4H), 1.99-1.92 (m, 2H), 1.69-1.27 (m, 57H), 0.87 (t, J=6.8 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.86, 172.45, 156.18, 135.55, 123.45, 75.24, 60.32, 56.68, 55.83, 40.72, 40.36, 34.40, 34.09, 31.79, 31.29, 29.92, 29.49, 29.41, 29.26, 29.17, 28.96, 28.55, 27.65, 26.49, 26.30, 25.41, 25.02, 24.79, 22.71, 20.12, 14.19.

Molecular weight for $\text{C}_{51}\text{H}_{95}\text{N}_2\text{O}_8$ (M+H)⁺ Calc. 863.71, Found 863.6.

Compound 105: To a solution of compound 104 (525 mg, 0.608 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (2 mL) at 0° C. The reaction mixture was stirred at 0° C. for 1 hour and at room temperature for 3 hours. The reaction mixture was evaporated and co-evaporated with toluene 3 times then dried in vacuo overnight to give compound 105 (603 mg, 0.603 mmol calculated as 2 TFA salt, quantitatively, R_f =0.24 developed with 8% MeOH in CH_2Cl_2).

^1H NMR (400 MHz, CDCl_3) δ 8.06 (brs, 1H), 5.68-5.61 (m, 2H), 5.55-5.49 (m, 2H), 4.87-4.81 (m, 1H), 4.62 (d, J=6.8 Hz, 4H), 4.28 (brs, 3H), 3.20-3.02 (m, 6H), 2.82 (d, J=4.0 Hz, 3H), 2.45-2.40 (m, 2H), 2.30 (t, J=7.4 Hz, 4H), 2.12-2.00 (m, 6H), 1.78-1.22 (m, 52H), 0.88 (t, J=6.8 Hz,

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6H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.04, 172.08, 161.84, 161.47, 135.63, 123.44, 117.60, 114.71, 75.56, 60.41, 55.69, 55.27, 39.94, 39.64, 34.44, 34.06, 31.82, 30.72, 29.53, 29.43, 29.28, 29.19, 29.00, 27.69, 26.58, 25.42, 25.27, 25.05, 24.60, 23.06, 22.75, 19.00, 14.22.

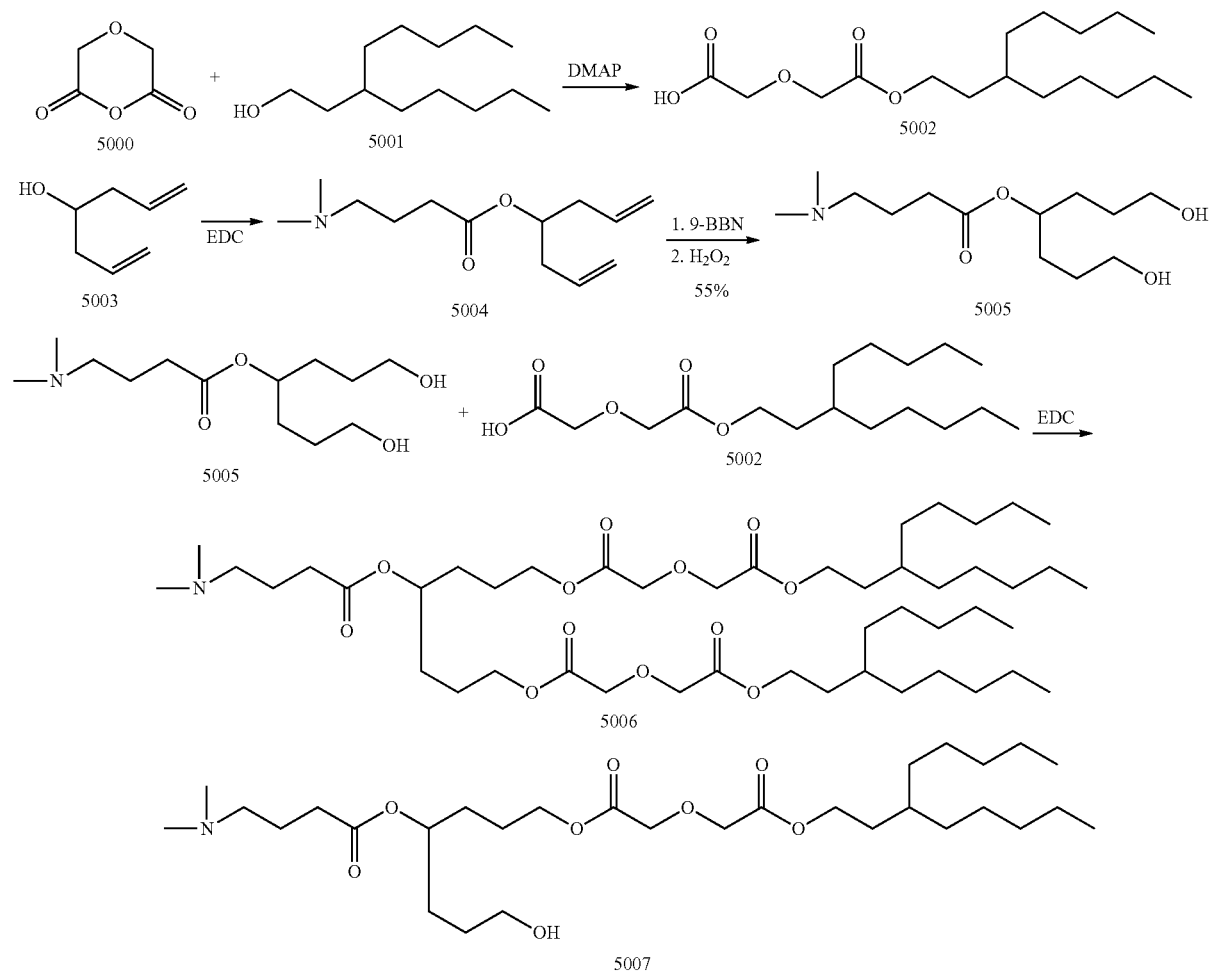
Molecular weight for $\text{C}_{46}\text{H}_{87}\text{N}_2\text{O}_6$ (M+H)⁺ Calc. 763.66, Found 763.4.

Compound 106: To a solution of 105 (23.8 mg, 0.0240 mmol, calculated as 2TFA salt) in CH_2Cl_2 (1 mL) and Et_3N (0.050 mL, 0.360 mmol) was added a solution of BODIPY® 493/503 (10 mg, 0.0240 mmol, Life Technology #D2191) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 1 h. The reaction mixture was loaded onto silica gel column chromatography and eluted with 0-5% MeOH in CH_2Cl_2 . The product color fractions were collected (5% MeOH in CH_2Cl_2 , R_f =0.36) to give 106 (26 mg, 0.024 mmol, quantitatively).

^1H NMR (400 MHz, CDCl_3) δ 6.05 (s, 2H), 5.67-5.61 (m, 2H), 5.54-5.48 (m, 2H), 4.85-4.82 (m, 1H), 4.61 (d, J=6.8 Hz, 4H), 3.37-3.32 (m, 2H), 3.27-3.22 (m, 2H), 2.51-2.44 (m, 17H), 2.34-2.27 (m, 8H), 2.12-2.06 (m, 4H), 1.60-1.21 (m, 52H), 0.88 (t, J=6.8 Hz, 6H).

Molecular weight for $\text{C}_{62}\text{H}_{104}\text{BF}_2\text{N}_4\text{O}_7$ (M+H)⁺ Calc. 1065.80, Found 1065.5.

Example 34: Multi-Ester Containing Lipids and Acetal Linked Lipids



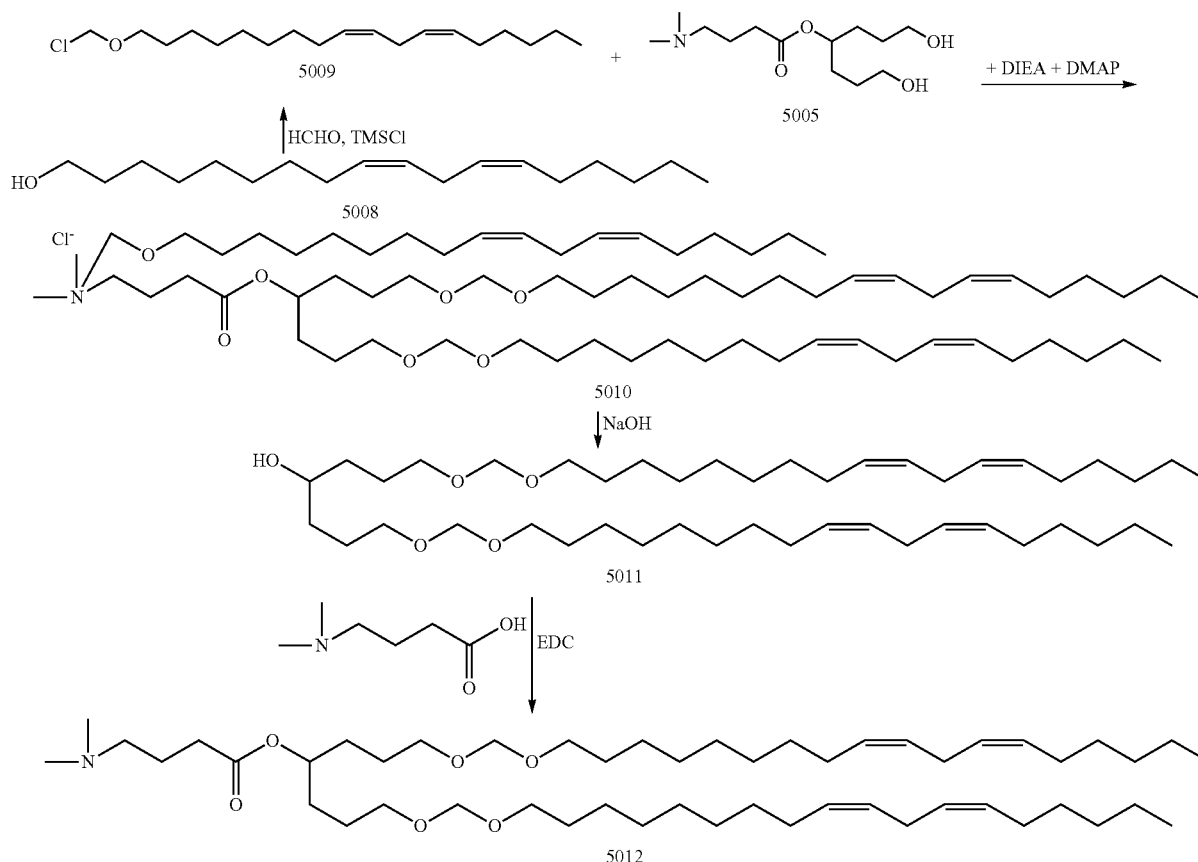
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Synthesis of compound 5002: To a stirred solution of alcohol 5001 (1.0 g, 5.15 mmol), Glycolic anhydride 5000 (5.66 mmol) in DCM (20 mL) was added DMAP (1.26 g, 10.41 mmol) and stirred at room temperature for 48 h. The

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chromatography to get 5006 (0.1 g, 12%) and 5007 (0.2 g, 36%). LCMS for compound 5006: Calculated: 857.62 (M^+), Found: 858.5 ($M^{30}+1$), 880.5 (M^++Na). LCMS for compound 5007: Calculated: 559.4 (M^+), Found: 560.4 ($M^{30}+1$).



reaction mixture was concentrated followed by column purification gave the corresponding product 5002 (1.4 g, 86%) as DMAP salt. LCMS: Calculated: 316.22 (M^+), Found: 315.1 (M^+-1).

Synthesis of compound 5004: To a stirred solution of alcohol 5003 (5.0 g, 44.6 mmol), 4-(Dimethylamino)butyric acid hydrochloride (8.1 g, 48.3 mmol) and EDC (10.3 g, 53.6 mmol) in DCM (100 mL) was added DIEA (23 g, 178.3 mmol) and stirred at room temperature overnight. After usual work up, the crude product was purified by column chromatography (9.0 g, 90%).

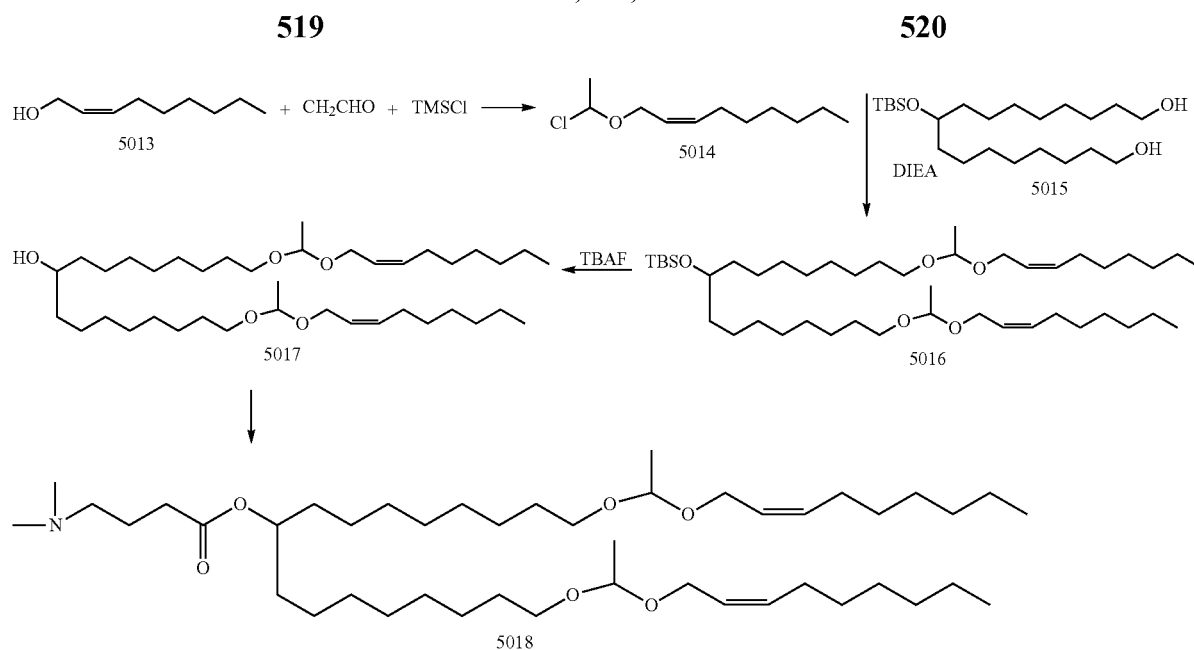
Synthesis of compound 5005: To a stirred solution of diene 5004 (4.0 g, 18 mmol) in 10 mL of THF was added 9-BBN and stirred overnight. To the above solution was added 6.6 mL of 3M NaOAc and 7.4 mL of 30% H_2O_2 at 0-5° C. The reaction mixture was stirred at room temperature overnight. After usual work up, the crude material was purified by column chromatography to get 5005 (2.6 g, 55%) as viscous oil. LCMS: Calculated: 261.19 (M^+), Found: 262.1 (M^++1).

Synthesis of compound 5006 and 5007: To a stirred solution of diene 5005 (260 mg, 1 mmol), acid 5002 (1.0 g, 2.28 mmol), EDC (387 mg, 2 mmol) in 10 mL of DCM was added DIEA (516 mg, 4 mmol) and stirred overnight. After usual work up, the crude material was purified by column

Synthesis of compound 5011: To a stirred solution of alcohol 5008 (2.66 g 10 mmol) in 5 mL of Chlorotrimethylsilane was added paraformaldehyde (0.3 g, 10 mmol) and stirred at room temperature overnight. The excess Chlorotrimethylsilane was evaporated followed by drying under reduced pressure gave the corresponding product 5009 and used for next step without purification. The compound 5009 was added dropwise to the solution of diol (261 mg, 1 mmol), DIEA (2.5 g, 19.4 mmol) and DMAP (20 mg, 0.16 mmol) in DCM (10 mL) and stirred overnight. Concentration of the solvent gave the crude product 5010, which was dissolved in 5 mL of THF and 2 mL of 1N NaOH was added and stirred for 2 days at room temperature. After usual work up, the crude material was purified by column chromatography to get the corresponding product 5011 (200 mg, 28%). LCMS for compound 5010: Calculated: 1131.95 (M^+), Found: 1096.98 (M^+-Cl^-). LCMS for compound 5011: Calculated: 704.63 (M^+), Found: 727.5 (M^++Na).

Synthesis of compound 5012: To a stirred solution of alcohol 5011 (200 mg, 0.284 mmol), 4-(Dimethylamino)butyric acid hydrochloride (103 mg, 0.57 mmol), EDC (109 mg, 0.57 mmol) in 10 mL of DCM was added DIEA (294 mg, 4 mmol) and stirred overnight. After usual work up, the crude material was purified by column chromatography to get 5012 (190 mg, 85%). LCMS for compound 5012: Calculated: 817.72 (M^+), Found: 818.5 (M^++Na).

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Synthesis of compound 5016: To a stirred solution of alcohol 5013 (1.0 g 7.03 mmol) in 5 mL of Chlorotrimethylsilane was added acetaldehyde (0.3 g, 7.03 mmol) and stirred at room temperature for 2 h. The excess Chlorotrimethylsilane was evaporated followed by drying under reduced pressure gave the corresponding product 5014 and used for next step without purification. The compound 5014 was added dropwise to the solution of diol 5015 (223 mg, 0.55 mmol), DIEA (2 mL g, 11.5 mmol) and DMAP (20 mg, 0.16 mmol) in DCM (10 mL) and stirred overnight. 10 mL of water was added followed by extraction with DCM (3×30 mL), washed with water, saturated NaHCO₃, brine and dried over anhydrous Na₂SO₄. Concentration of the solvent gave the crude product, which was used for the next step without purification. LCMS for compound 5016: Calculated: 738.66 (M⁺), Found: 761.5 (M⁺+Na).

Synthesis of compound 5017: To a stirred solution of alcohol 5016 in 5 mL of THF was added 0.54 mL of 1M TBAF in THF (0.54 mmol) and stirred for 2 days at room temperature. After usual work up, the crude material was purified by column chromatography to get 5017. However, it contains some inseparable impurity and hence used for next step without further purification. LCMS for compound 5017: Calculated: 624.57 (M⁺), Found: 647.5 (M⁺+Na).

Synthesis of compound 5018: To a stirred solution of alcohol 5017 (0.55 mmol), 4-(Dimethylamino)butyric acid hydrochloride (116 mg, 0.64 mmol), EDC (123 mg, 0.64 mmol) in 10 mL of DCM was added DIEA (165 mg, 1.28 mmol) and stirred for 2 days. After usual work up, the crude material is purified by column chromatography (0-10% MeOH in 1% Et₃N containing DCM) to get 5018 (300 mg, 75% from 5015). LCMS for compound 5018: Calculated: 737.65 (M⁺), Found: 738.6 (M³⁰+1), 760.5 (M⁺+Na⁺).

Example 35: Preparation of Lipid Nanoparticles

The cationic lipids described herein are used to formulate liposomes containing the AD-1661 duplex (shown in the table below) using an in-line mixing method as described in International Publication No. WO 2010/088537, which is

incorporated by reference in its entirety. The lipid nanoparticles had the formulation shown in the table below.

Component	Mole Percentage (Based on 100% of the lipid components in the LNP)
Cationic lipid	50%
Distearoylphosphatidylcholine (DSPC)	10%
Cholesterol	38.5%
1-(monomethoxy-polyethyleneglycol)- 2,3-dimyristoylglycerol (PEG-DMG) (with an average PEG molecular weight of 2000)	1.5%
siRNA (AD-1661)	—

The siRNA AD-1661 duplex has the sequence shown below.

Duplex	Sequence 5'-3'	SEQ ID NO: Target
AD-1661	GGAfUfCAfUfCfUfCAAGfUfCfUfUfAfcdT	1 FVII
	GfUAAGAfCfUfUfGAGAfUGAfUfCfCdTsdT	2

Lower case is 2'OMe modification and Nf is a 2'F modified nucleobase, dT is deoxythymidine, s is phosphothioate

The lipid nanoparticles was prepared as follows. Cationic lipid, DSPC, cholesterol, and PEG-DMG in the ratio recited in the table above were solubilized in ethanol at a total lipid concentration of 25 mg/mL.

A siRNA stock solution was prepared by solubilizing the siRNA AD-1661 in a low pH acetate or citrate buffer (pH=4) at 0.8 mg/mL.

The stock solutions should be completely clear and the lipids should be completely solubilized before combining with the siRNA. Therefore, if it was determined appropriate, the stock solutions were heated to completely solubilize the lipids.

The individual stock solutions were combined by pumping each solution to a T-junction (i.e., by in-line mixing).

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Specifically, the ethanol solution (at 5 ml/min, via 0.01 in. PEEK tube) and aqueous buffer solution (at 15 mL/min, via 0.02 in. PEEK tube) were mixed through a T-junction (PEEK Tee body, IDEX).

After the T-junction a single tubing is placed where the combined stream will emit. Ethanol is removed and exchanged for PBS by dialysis. The lipid formulations are then concentrated using centrifugation or diafiltration to an appropriate working concentration.

Lipid nanoparticles containing the cationic lipids listed in the table in Example 36 were prepared as described above.

Example 36: Efficacy of Lipid Nanoparticles

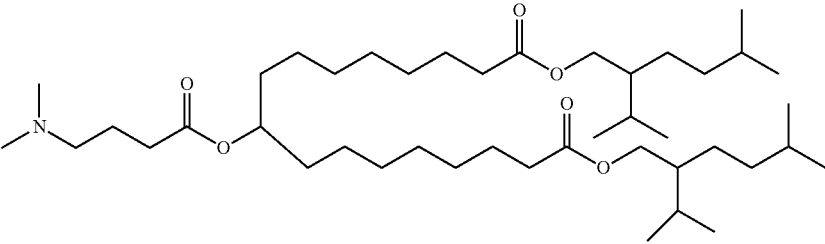
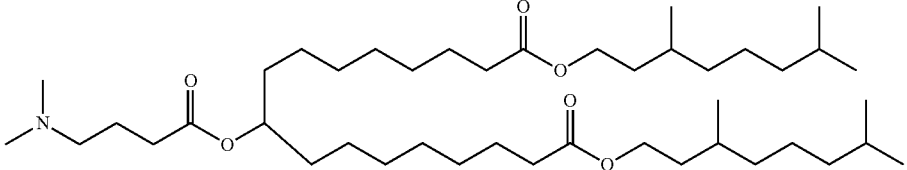
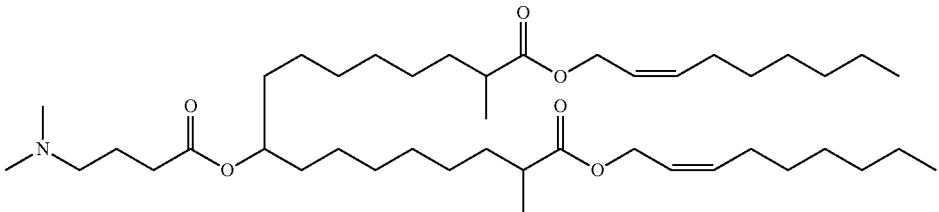
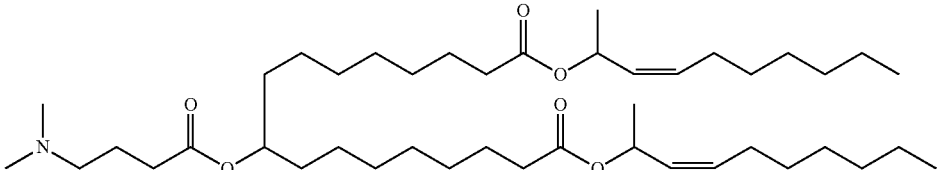
Factor VII (FVII), a prominent protein in the coagulation cascade, is synthesized in the liver (hepatocytes) and secreted into the plasma. FVII levels in plasma can be determined by a simple, plate-based colorimetric assay. As such, FVII represents a convenient model for determining siRNA-mediated downregulation of hepatocyte-derived proteins.

Test formulations of the lipid nanoparticles prepared in Example 35 were initially assessed for their FVII knockdown in female 7-9 week old, 15-25 g, female C57Bl/6 mice at 0.1, 0.3, 1.0 and 5.0 mg/kg with 3 mice per treatment group. All studies included animals receiving either phosphate-buffered saline (PBS, control group) or a benchmark formulation. Formulations were diluted to the appropriate

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concentration in PBS immediately prior to testing. Mice were weighed and the appropriate dosing volumes calculated (10 μ l/g body weight). Test and benchmark formulations as well as PBS (for control animals) were administered intravenously via the lateral tail vein. Animals were anesthetized 24 hours later with an intraperitoneal injection of ketamine/xylazine and 500-700 μ l of blood was collected by cardiac puncture into serum separator tubes (BD Microtainer). Blood was centrifuged at 2,000 \times g for 10 minutes at 15° C. and serum was collected and stored at -70° C. until analysis. Serum samples were thawed at 37° C. for 30 minutes, diluted in PBS and aliquoted into 96-well assay plates. Factor VII levels were assessed using a chromogenic assay (Biophen FVII kit, Hyphen BioMed) according to the manufacturer's instructions and absorbance was measured in a microplate reader equipped with a 405 nm wavelength filter. Plasma FVII levels were quantified and ED₅₀ values (dose resulting in a 50% reduction in plasma FVII levels compared to control animals) were calculated using a standard curve generated from a pooled sample of serum from control animals. Those formulations of interest showing high levels of FVII knockdown (ED₅₀ < 0.1 mg/kg) were re-tested in independent studies at a lower dose range to confirm potency and establish ED₅₀ levels.

The following table shows ED₅₀ values for some of the cationic lipids described herein. Two asterisks (**) indicates an ED₅₀ value between 0.001 and 0.10. One asterisk (*) indicates an ED₅₀ value greater than 0.10.

ED ₅₀	Cationic Lipid
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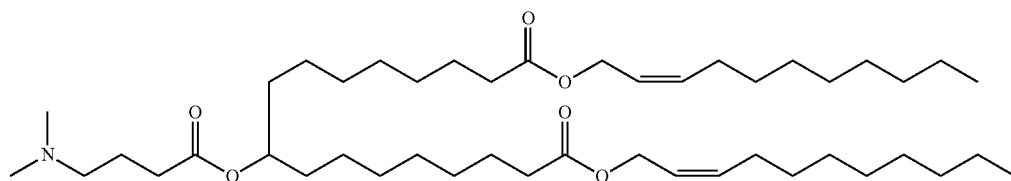
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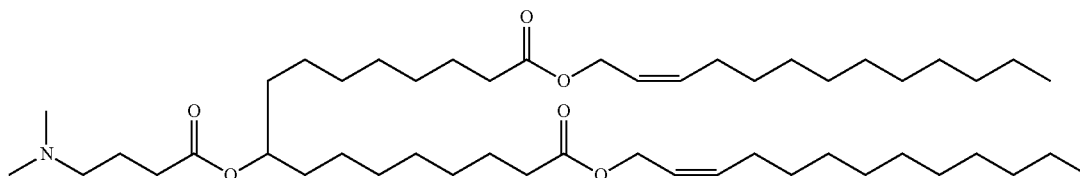
ED₅₀

Cationic Lipid

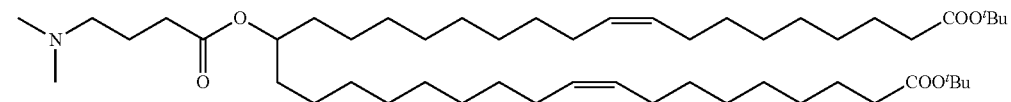
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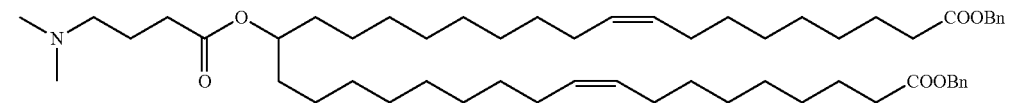
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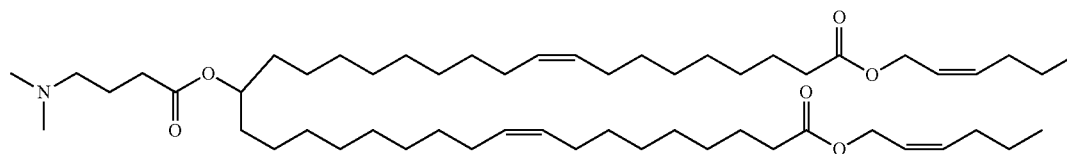
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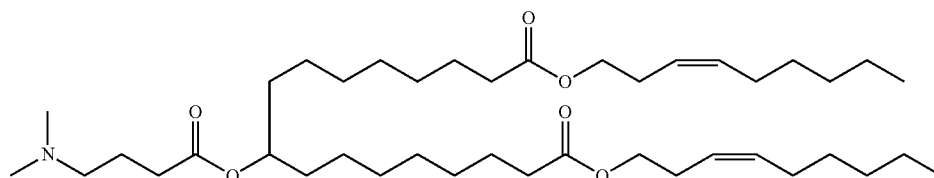
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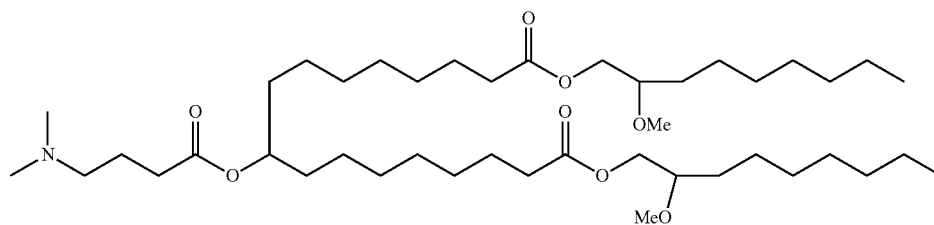
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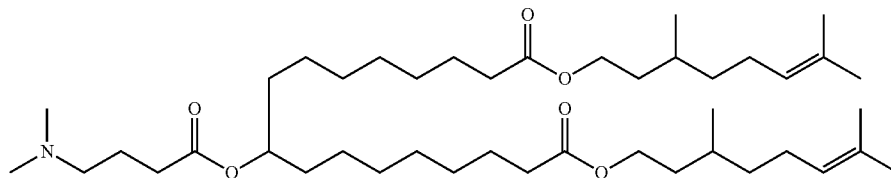
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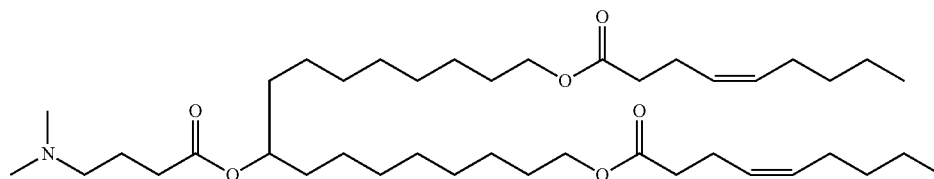
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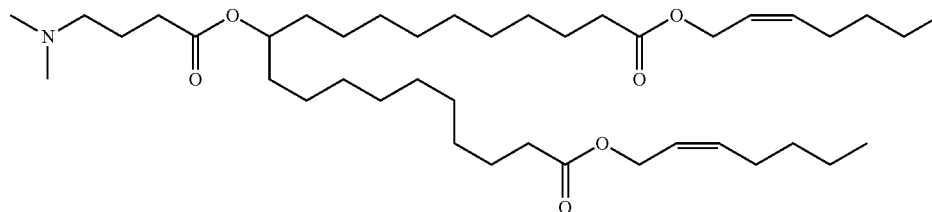
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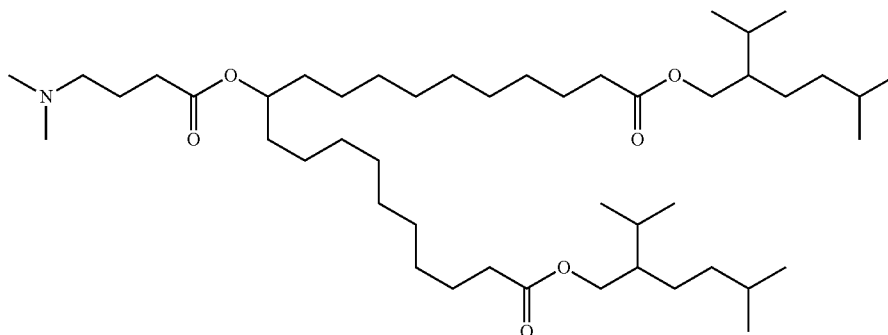
ED₅₀

Cationic Lipid

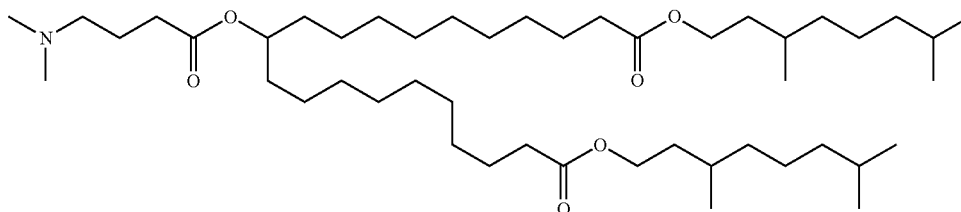
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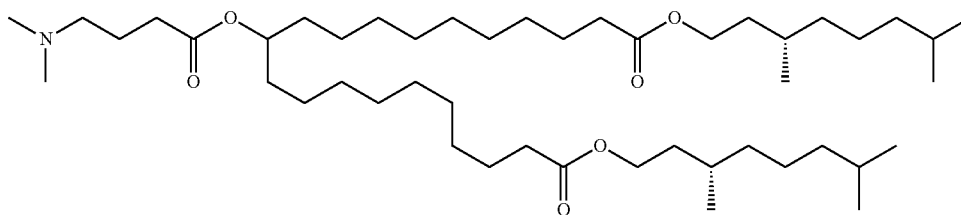
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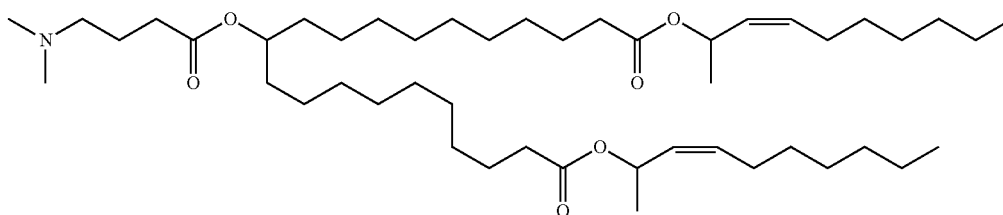
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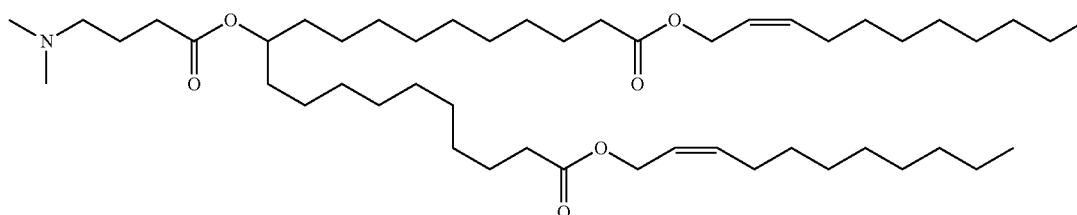
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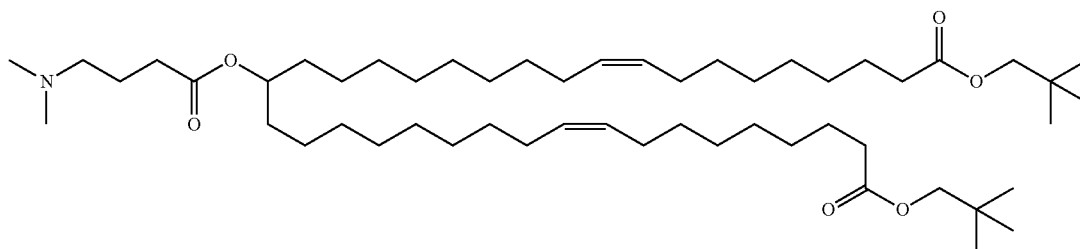
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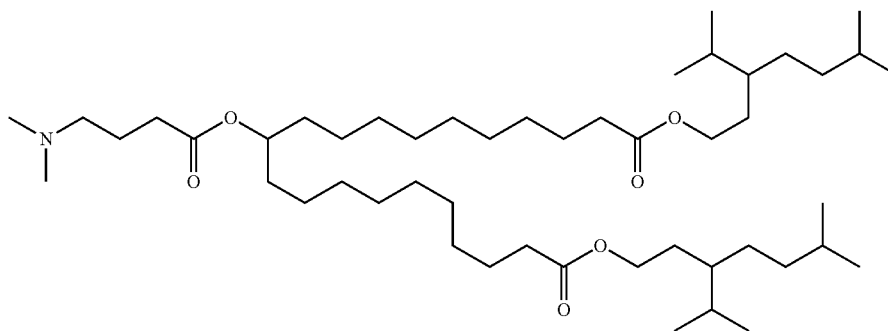
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Cationic Lipid

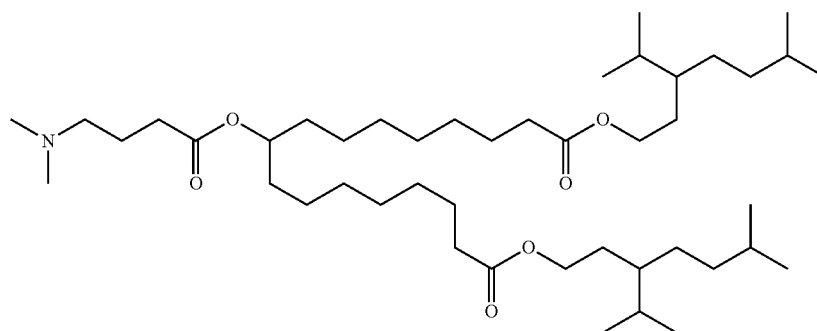
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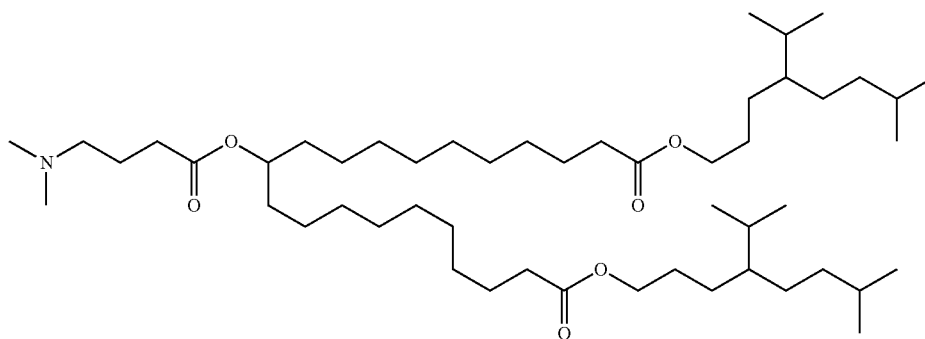
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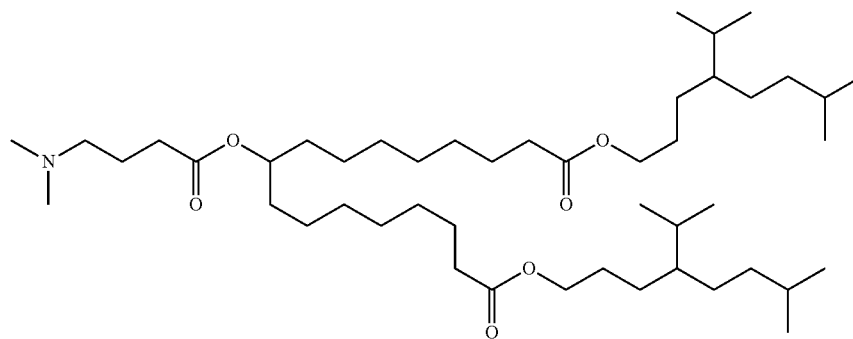
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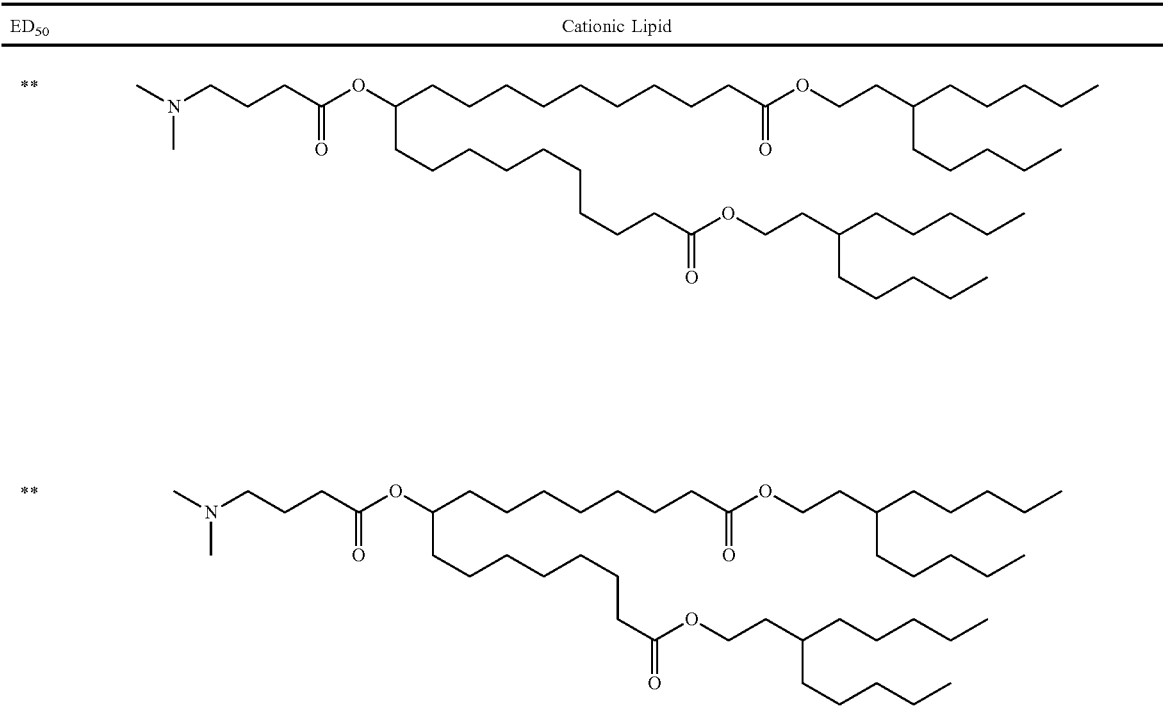


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Example 37: Hydrophobicity and Stability

The log P values for the biodegradable cationic lipids listed in the table below were calculated using the software 35 available at <http://www.molinspiration.com/services/logp.html> from Molinspiration Cheminformatics of Slovensky Grob, Slovak Republic.

Furthermore, the HPLC retention time for each biodegradable cationic lipid was measured in lipid nanoparticles 40 prepared from them. The lipid nanoparticles were prepared as described in Example 35 using AD-1661 as the payload. The retention times are reported in the table below relative to the retention time for cholesterol.

The HPLC buffer used was a mixture of two solutions 45 (Solution #1 and Solution #2).

Solution #1: 80% methanol/20% 10 mM NH₄HCO₃

Solution #2: 80% methanol/20% isopropanol

The ratios of the two solutions in the mixture changed 50 over time as indicated in the table below.

Time (mm)	Solution #1 (vol %)	Solution #2 (vol %)
0	70	30
4	10	90
6	10	90
6.1	70	30
8	70	30

The size of the lipid nanoparticles was measured before and after undergoing dialysis overnight. In general, greater changes in lipid nanoparticle size are indicative of lesser stability.

Dynamic laser light scattering was used to determine the lipid nanoparticle size (expressed as the intensity weighted diameter) with a Zetasizer (Malvern Instruments, Inc. of Westborough, Mass.). All measurements were made at 532 nm wavelength at the scattering angle of 173° using normal resolution mode as the analysis model.

The results of these experiments are provided in the table below.

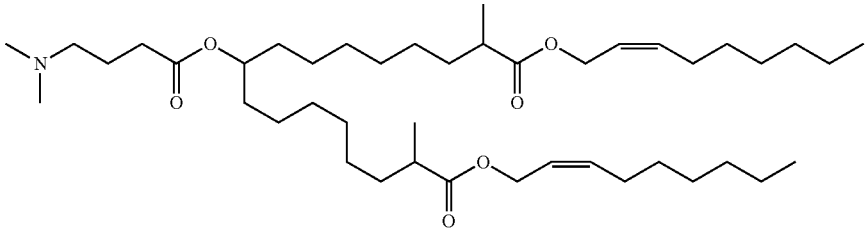
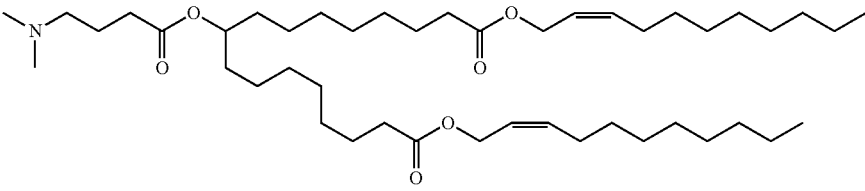
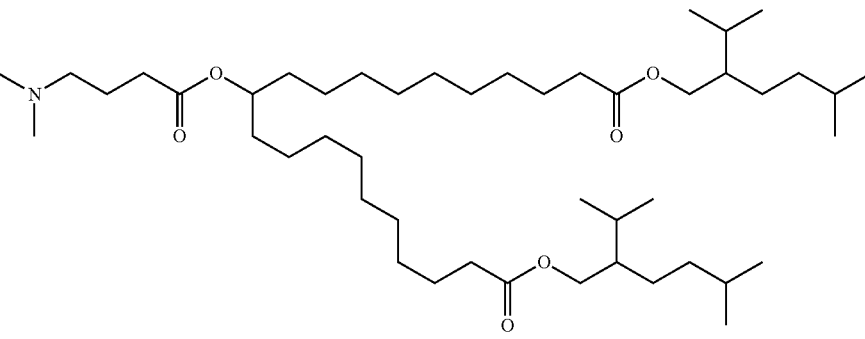
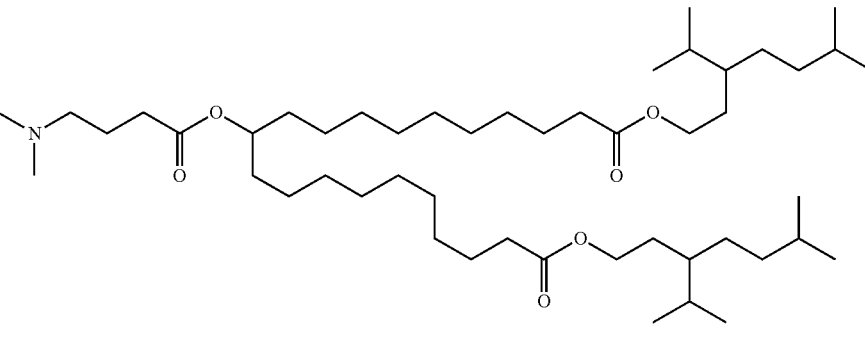
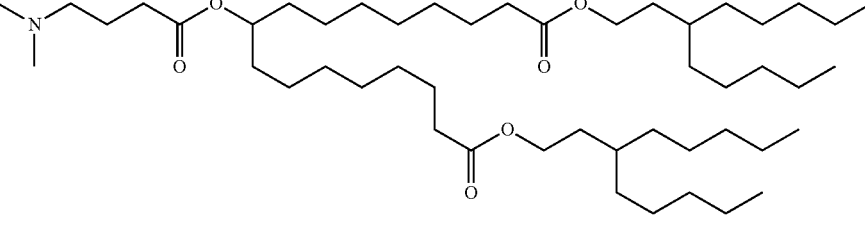
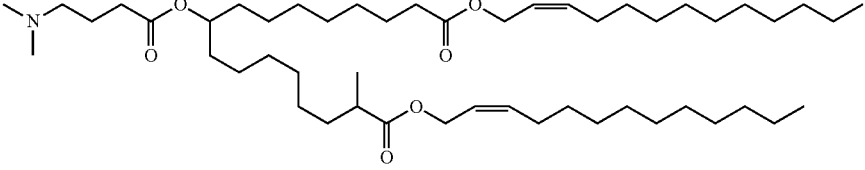
Cationic Lipid	t(lipid) – logP	t(chol)	LNPs Size (nm) change
	9.647	-1.4	170 -> 260

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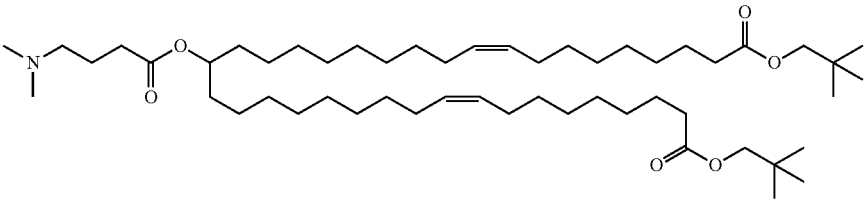
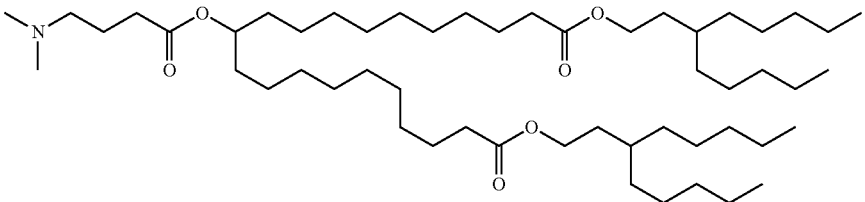
Cationic Lipid	logP	t(lipid) - t(chol)	LNPs Size (nm) change
	9.972	0.848	73 -> 77
	10.093	1.44	60 -> 67
	10.201	1.751	59 -> 60
	10.259	2.106	
	10.313	2.365	56 -> 56
	10.315	2.219	68 -> 67

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Cationic Lipid	logP	t(lipid) – t(chol)	LNPs Size (nm) change
	10.416	2.707	
	10.495	3.178	

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the

specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

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21

What is claimed is:

1. A cationic lipid comprising a primary group and two biodegradable hydrophobic tails, wherein (a) the primary group includes a head group and a central moiety to which both the biodegradable hydrophobic tails and the head group are directly bonded, wherein the primary group has a protonatable group having a pK_a of from about 4 to about 11, (b) the cationic lipid has an in vivo half life ($t_{1/2}$) of less than about 3 hours in the liver, (c) the cationic lipid has a logP value of at least 10.1, and (d) each biodegradable hydrophobic tail has the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain),

wherein in at least one biodegradable hydrophobic tail, (i) the terminal hydrophobic chain in the hydrophobic tail is a branched alkyl group, where the branching occurs at the α -position relative to the biodegradable group; (ii) the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms; (iii) the at least one biodegradable hydrophobic tail has the formula $-R^{12}-M^1-R^{13}$, where R^{12} is a C_4 - C_{14} alkylene or C_4 - C_{14} alkenylene, M^1 is the biodegradable group, and R^{13} is a branched C_{10} - C_{20} alkyl; and (iv) the total carbon atom content of the tail $-R^{12}-M^1-R^{13}$ is 21 to 26.

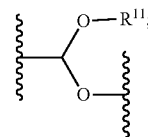
2. The cationic lipid of claim 1, wherein the central moiety is selected from the group consisting of a central carbon atom, a central nitrogen atom, a central carbocyclic group, a central aryl group, a central heterocyclic group, and a central heteroaryl group.

3. The cationic lipid of claim 1, wherein the biodegradable group is $-OC(O)-$.

4. The cationic lipid of claim 1, wherein the biodegradable group is $-C(O)O-$.

5. The cationic lipid of claim 1, wherein the chain length of $-R^{12}-M^1-R^{13}$ is at most 21 atoms from the first carbon atom after the primary group to a terminus of the tail.

6. The cationic lipid of claim 1, wherein each biodegradable group is independently selected from the group consisting of $-OC(O)-$, $-C(O)O-$, $-SC(O)-$, $-C(O)S-$, $-OC(S)-$, $-C(S)O-$, $-S-S-$, $-C(R^5)=N-$, $-N=C(R^5)-$, $-C(R^5)=N-O-$, $-O-N=C(R^5)-$, $-C(O)(NR^5)-$, $-N(R^5)C(O)-$, $-C(S)(NR^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)N(R^5)-$, $-OC(O)O-$, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, $-OC(O)(CR^3R^4)C(O)-$, or



each occurrence of R^3 and R^4 is, independently, H, halogen, OH, alkyl, alkoxy, $-NH_2$, R^{10} , alkylamino, or dialkylamino;

each occurrence of R^5 is, independently, H or alkyl; each occurrence of R^{10} is, independently, selected from polyethylene glycol (PEG) and polymers based on

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poly(oxazoline), poly(ethylene oxide), poly(vinyl alcohol), poly(glycerol), poly(N-vinylpyrrolidone), poly [N-(2-hydroxypropyl) methacrylamide] and poly (amino acid)s, wherein (i) the PEG or polymer is linear or branched, (ii) the PEG or polymer is polymerized by n subunits, (iii) n is a number-averaged degree of polymerization between 10 and 200 units and (iv) the compound of formula has at most two R¹⁰ groups; and R¹¹ is a C₂-C₈ alkyl or C₂-C₈ alkenyl.

7. The cationic lipid of claim 1, wherein in both biodegradable hydrophobic tails,

- (i) the terminal hydrophobic chain in the hydrophobic tail is a branched alkyl group, where the branching occurs at the α -position relative to the biodegradable group;
- (ii) the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms;
- (iii) the biodegradable hydrophobic tail has the formula —R¹²-M¹-R¹³, where R¹² is a C₄-C₁₄ alkylene or C₄-C₁₄ alkenylene, M¹ is the biodegradable group, and R¹³ is a branched C₁₀-C₂₀ alkyl; and
- (iv) the total carbon atom content of the tail —R¹²-M¹-R¹³ is 21 to 26.

8. The cationic lipid of claim 1, wherein the cationic lipid has a logP value of at least about 10.2.

9. The cationic lipid of claim 1, wherein the cationic lipid has a $t_{lipid}-t_{chol}$ value of at least about 1.75.

10. The cationic lipid of claim 1, wherein the cationic lipid has a pKa value of from about 4 to about 7.

11. The cationic lipid of claim 10, wherein the cationic lipid has a pKa value of from about 6 to about 6.5.

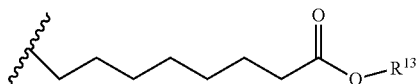
12. The cationic lipid of claim 1, wherein the cationic lipid has a logP value of at least about 10.1 and/or a $t_{lipid}-t_{chol}$ value of at least about 1.4.

13. A cationic lipid comprising (i) a head group, (ii) two hydrophobic tails, each of the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain), and (iii) a linker group bound to the head group and the hydrophobic tails, wherein the cationic lipid has:

- (i) a log P value of at least 10.1;
- (ii) a pKa of from about 4 to about 7;
- (iii) for at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms;
- (iv) for at least one hydrophobic tail, the total number of carbon atoms in the hydrophobic tail is from 21 to 26;
- (v) for at least one hydrophobic tail, the number of carbon atoms between the linker group and the biodegradable group in the hydrophobic tail ranges from about 5 to about 10;
- (vi) for at least one hydrophobic tail, the total number of carbon atoms between the linker group and a terminus of the hydrophobic tail is from about 15 to about 20;
- (vii) for at least one hydrophobic tail, the terminal hydrophobic chain in the hydrophobic tail is a branched alkyl or branched alkenyl group; and
- (viii) when formulated as a lipid nanoparticle, the cationic lipid has an in vivo half life ($t_{1/2}$) in the liver of less than about 3 hours.

14. The cationic lipid of claim 1, wherein the branched alkyl group has only one carbon atom which is bound to three other carbon atoms.

15. The cationic lipid of claim 1, wherein the at least one biodegradable hydrophobic tail has the formula



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where R¹³ is a branched alkyl group having from 13 to 17 carbon atoms, and the total carbon length of the tail from the first carbon to a terminus of the tail is at most 20.

16. A method of delivering a nucleic acid molecule comprising administering to a subject a lipid particle comprising:

- (i) a nucleic acid molecule,
- (ii) a cationic lipid according to claim 1, and
- (iii) a PEG lipid.

17. The method of claim 16, wherein the pKa of the cationic lipid is 6.0 to 7.0.

18. A cationic lipid comprising a primary group and two biodegradable hydrophobic tails, wherein

- the primary group comprises (i) a head group that optionally comprises a primary, secondary, or tertiary amine, and (ii) a central moiety to which the head group and the two biodegradable hydrophobic tails are directly bonded;

the central moiety is a central carbon or nitrogen atom; each biodegradable hydrophobic tail independently has the formula -(hydrophobic chain)-(biodegradable group)-(hydrophobic chain), wherein the biodegradable group is —OC(O)— or —C(O)O—;

for at least one biodegradable hydrophobic tail, the terminal hydrophobic chain in the biodegradable hydrophobic tail is a branched alkyl, where the branching occurs at the α -position relative to the biodegradable group and the biodegradable hydrophobic tail has the formula —R¹²-M¹-R¹³, where R¹² is a C₄-C₁₄ alkylene or C₄-C₁₄ alkenylene, M¹ is the biodegradable group, R¹³ is a branched C₁₀-C₂₀ alkyl, and the total carbon atom content of the tail —R¹²-M¹-R¹³ is 21 to 26;

in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms; and

the lipid has a pKa in the range of about 4 to about 11 and a logP of at least 10.1.

19. The cationic lipid of claim 18, wherein the biodegradable group is —OC(O)—.

20. The cationic lipid of claim 18, wherein the biodegradable group is —C(O)O—.

21. The cationic lipid of claim 18, wherein both biodegradable hydrophobic tails have the formula —R¹²-M¹-R¹³.

22. The cationic lipid of claim 18, wherein the chain length of —R¹²-M¹-R¹³ is at most 21 atoms from the first atom after the central moiety to a terminus of the tail.

23. The cationic lipid of claim 18, wherein the lipid has a pKa of from about 5 to about 7 when incorporated into a lipid particle.

24. The cationic lipid of claim 18, wherein, in at least one hydrophobic tail, the number of carbon atoms between the central moiety and the biodegradable group in the hydrophobic tail ranges from 5 to 10.

25. The cationic lipid of claim 18, wherein, in at least one hydrophobic tail, the total number of carbon atoms between the central moiety and a terminus of the hydrophobic tail ranges from 15 to 20.

26. The cationic lipid of claim 18, wherein in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 8 to 12 carbon atoms.

27. The cationic lipid of claim 26, wherein in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by 8 carbon atoms.

28. The cationic lipid of claim 18, wherein in both biodegradable hydrophobic tails,

US 11,246,933 B1

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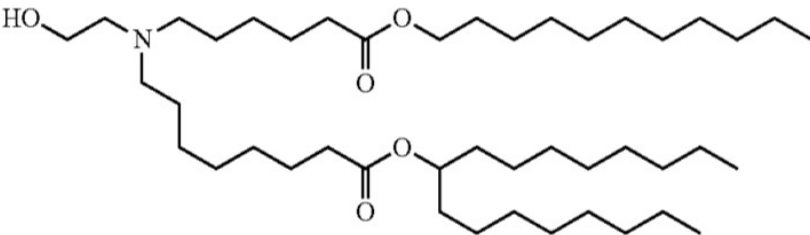
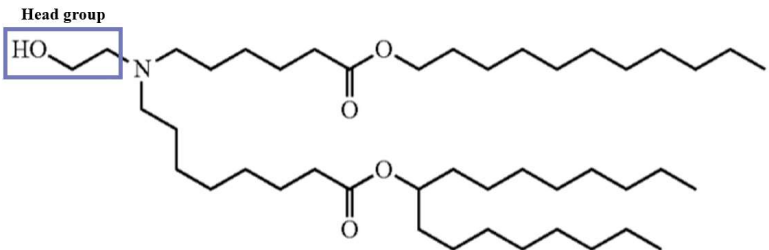
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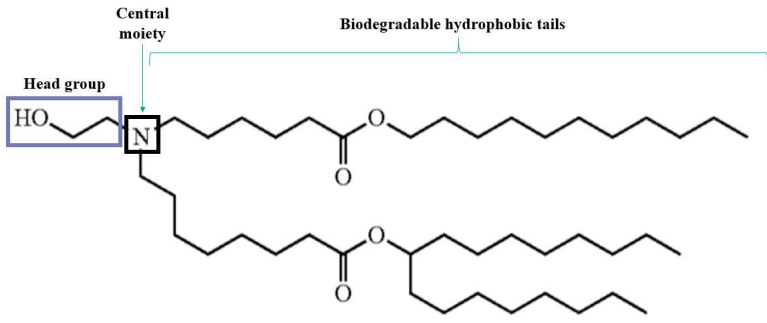
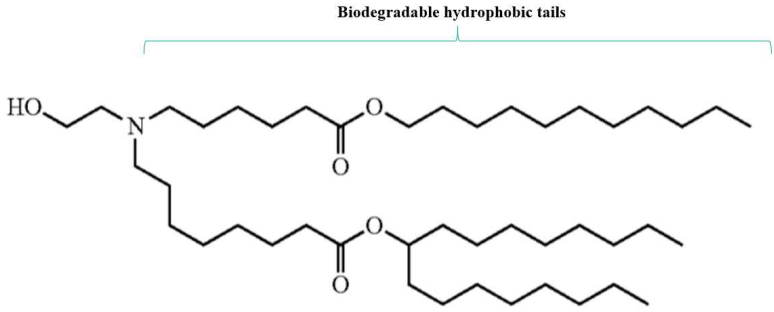
- (i) the terminal hydrophobic chain in the hydrophobic tail is a branched alkyl group, where the branching occurs at the α -position relative to the biodegradable group;
- (ii) the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms; 5
- (iii) the biodegradable hydrophobic tail has the formula $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$, where R^{12} is a $\text{C}_4\text{—C}_{14}$ alkylene or $\text{C}_4\text{—C}_{14}$ alkenylene, M^1 is the biodegradable group, and R^{13} is a branched $\text{C}_{10}\text{—C}_{20}$ alkyl; and
- (iv) the total carbon atom content of the tail $\text{—R}^{12}\text{—M}^1\text{—R}^{13}$ is 21 to 26. 10

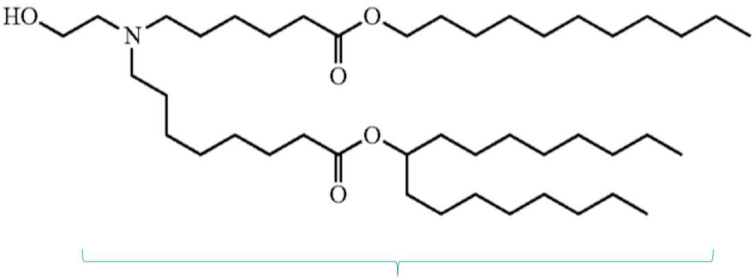
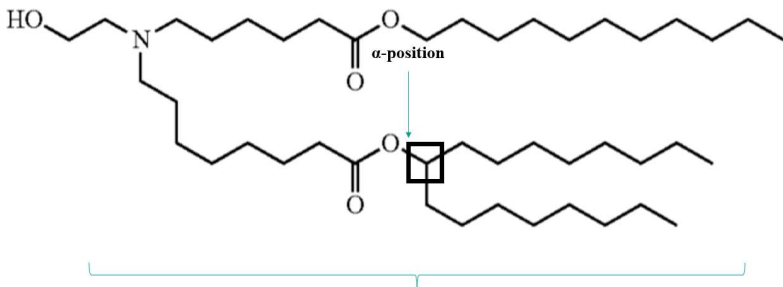
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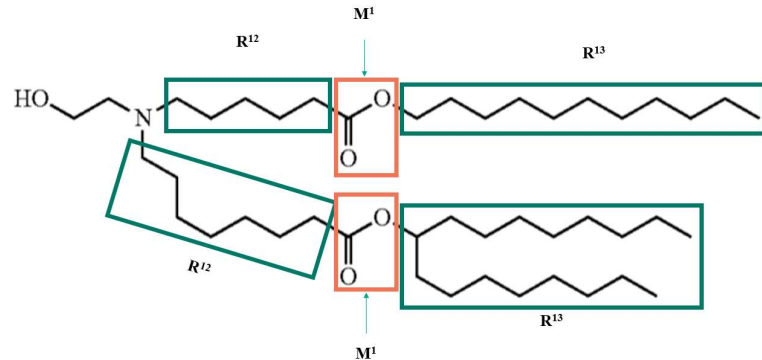
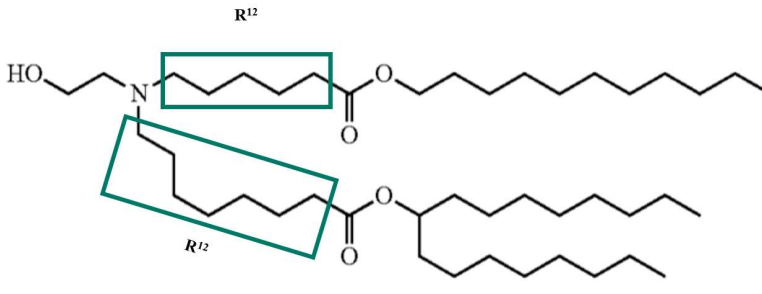
EXHIBIT 2

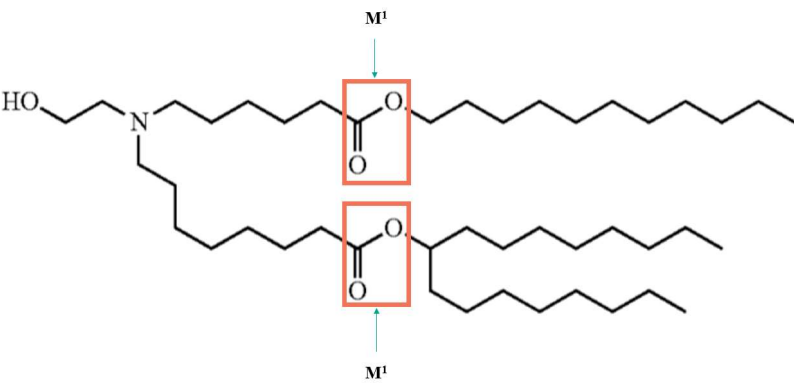
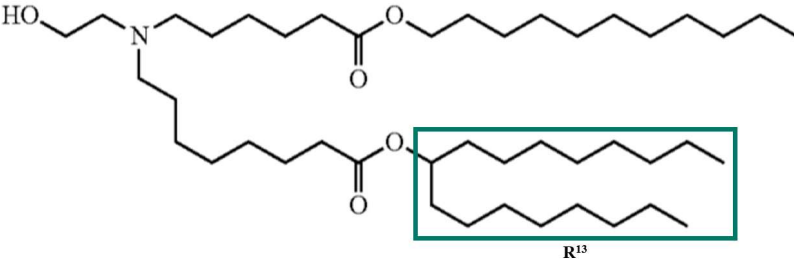
Preliminary Infringement Claim Chart for Claims 18, 20-22, and 24-27 of the '933 Patent

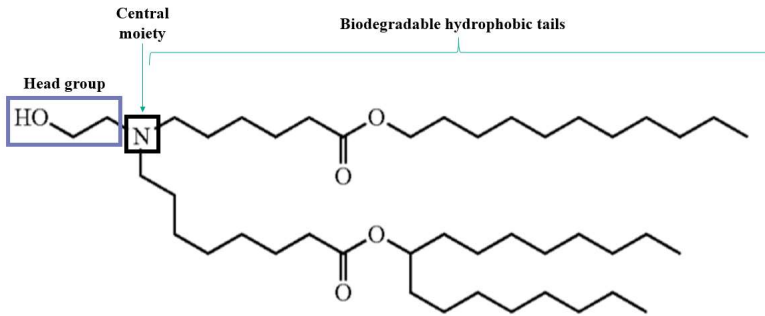
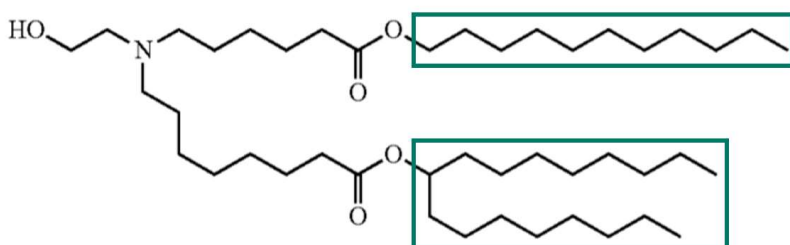
18.	A cationic lipid comprising a primary group and two biodegradable hydrophobic tails, wherein	<p>The Moderna vaccine uses the lipid SM-102. <i>See</i> Exhibit 5 at 11.</p> <p>Literature provides the following structure:</p>  <p><i>See</i> Exhibit 8 at 8 (Linde Schoenmaker, et al., <i>mRNA-lipid Nanoparticle COVID-19 Vaccines: Structure and Stability</i>, Int'l J. of Pharms. 601 (2021)).</p>
	the primary group comprises	
		<p>(i) a head group that optionally comprises a primary, secondary, or tertiary amine, and</p> <p>SM-102 has a head group:</p>  <p>Optional limitation for amine in the head group.</p>

	(ii) a central moiety to which the head group and the two biodegradable hydrophobic tails are directly bonded;	<p>SM-102 has a central moiety that is a nitrogen and the head group and both tails are directly bonded to it:</p> 
	the central moiety is a central carbon or nitrogen atom;	The central moiety of SM-102 is a nitrogen atom.
	each biodegradable hydrophobic tail independently has the formula - (hydrophobic chain)-(biodegradable group)-(hydrophobic chain), wherein the biodegradable group is -OC(O)- or -C(O)O-;	<p>SM-102 has biodegradable tails of the form: (hydrophobic chain)(biodegradable group)-(hydrophobic chain). The biodegradable group is C(O)O.</p> 

	<p>for at least one biodegradable hydrophobic tail, the terminal hydrophobic chain in the biodegradable hydrophobic tail is a branched alkyl,</p>	<p>The terminal hydrophobic chain in one of the biodegradable tails of SM-102 is a branched alkyl:</p>  <p style="text-align: center;">Branched biodegradable hydrophobic tail</p>
	<p>where the branching occurs at the α-position relative to the biodegradable group and</p>	<p>The branching in SM-102's terminal hydrophobic chain occurs at the α-position:</p>  <p style="text-align: center;">Branched biodegradable hydrophobic tail</p>

		<p>the biodegradable hydrophobic tail has the formula $-R^{12}-M^1-R^{13}$,</p>	<p>SM-102's biodegradable tails have the formula $-R^{12}-M^1-R^{13}$:</p> 
		<p>where R^{12} is a C₄-C₁₄ alkylene or C₄-C₁₄ alkenylene,</p>	<p>The R^{12} for the upper and lower chains of SM-102 are C₄-C₁₄ alkylens.</p> 

		M ¹ is the biodegradable group,	<p>M¹ for SM-102 is -C(O)O-, which is the biodegradable group:</p> 
		R ¹³ is a branched C ₁₀ -C ₂₀ alkyl, and	<p>The branched biodegradable tail of SM-102 has the structure:</p>  <p>R¹³ is a C₁₀-C₂₀ alkyl chain.</p>

		<p>the total carbon atom content of the tail $-R^{12}-M^1-R^{13}$ is 21 to 26;</p>	<p>The total carbon count is 21-26 for at least one tail $-R^{12}-M^1-R^{13}$ in SM-102:</p> 
	<p>in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 6 to 12 carbon atoms; and</p>	<p>For SM-102, a terminus is separated from the biodegradable group by from 6 to 12 carbon atoms for the top chain and by from 6 to 12 carbon atoms for the bottom chain.</p> 	

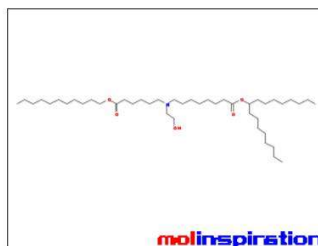
the lipid has a pKa in the range of about 4 to about 11 and a logP of at least 10.1

The pKa for SM-102 is 6.75. *See Exhibit 18 at 7 (Michael D. Buschmann, et al., Nanomaterial Delivery Systems for mRNA Vaccines, Vaccines 2021, 9, 65).*

The logP for SM-102 is 10.18. *See Exhibit 19 (Molinspiration logP Calculator, <http://www.molinspiration.com/services/logp.html>).*

molinspiration

originalSMILES CCCCCCCCCCCCOC(=O)CCCCN(CCCCCC(=O)OC(CCCCCC)CCCCCCC
 miSMILES: CCCCCCCCCCCCOC(=O)CCCCN(CCCCCC(=O)OC(CCCCCC)CCCCCCC



[Molinspiration property engine v2018.10](#)

miLogP	10.18
TPSA	76.08
atoms	50
Mw	710.18
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nOHNH	1
nviolations	2
nrotb	43
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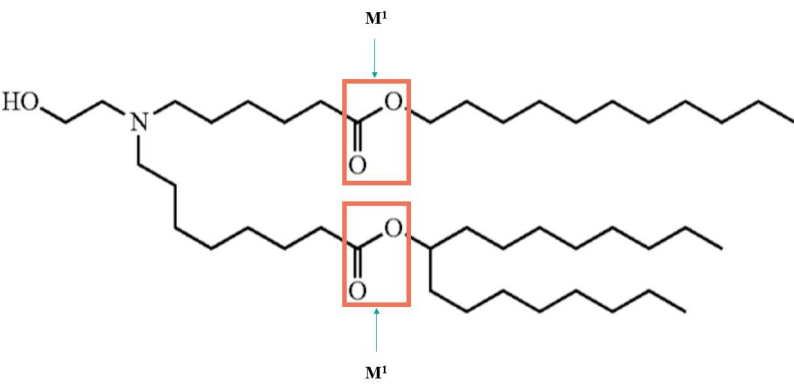
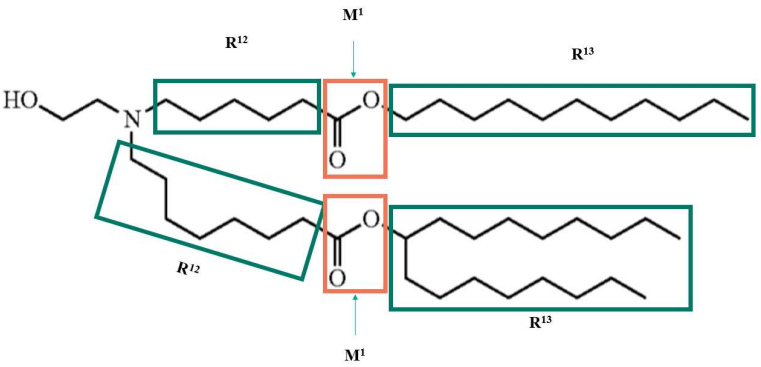
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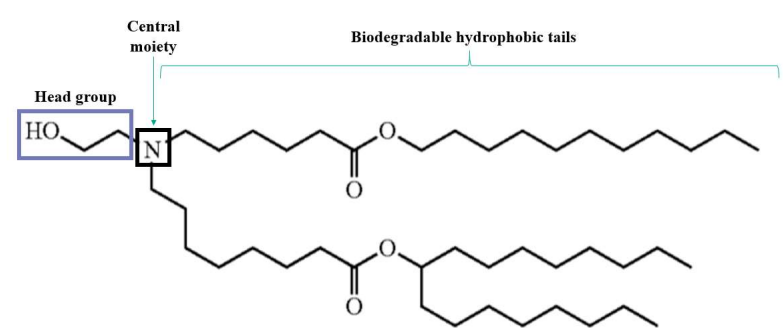
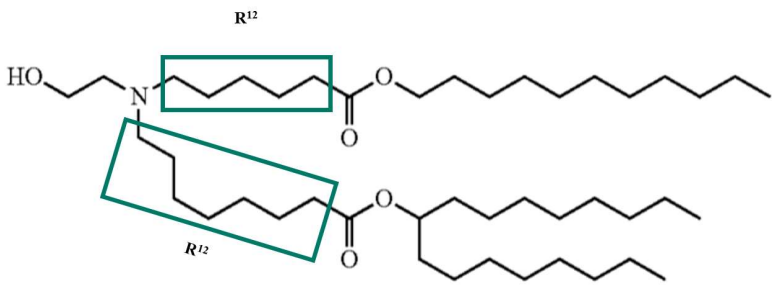
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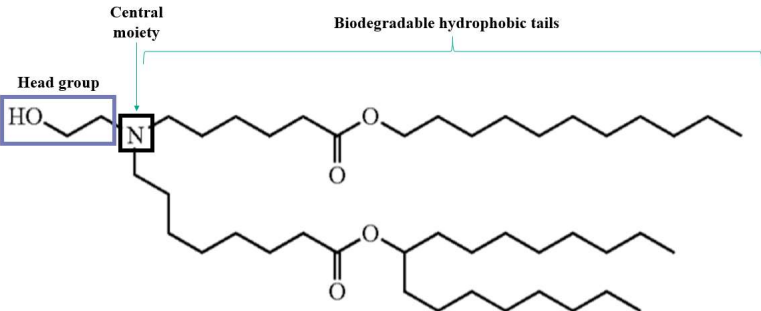
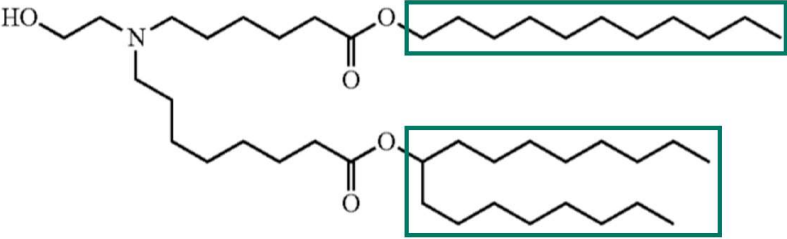
This was request 2 out of 1000 available this month for your site 65.96.110.54
 With technology from Molinspiration you can easily setup similar service also directly on your intranet.
 Comments or questions ? See our [FAQ](#) and do not hesitate to provide feedback or contact us by email !

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20.	The cationic lipid of claim 18, wherein the biodegradable group is $-C(O)O-$.	<p>M^1 for SM-102 is $-C(O)O-$, which is the biodegradable group.</p> 
21.	The cationic lipid of claim 18, wherein both biodegradable hydrophobic tails have the formula $-R^{12}-M^1-R^{13}$.	<p>The biodegradable tails of SM-102 have the formula $R^{12}-M^1-R^{13}$:</p> 

22.	The cationic lipid of claim 18, wherein the chain length of $-R^{12}-M^1-R^{13}$ is at most 21 atoms from the first atom after the central moiety to a terminus of the tail.	<p>For SM-102, it is at most 21 atoms from the first atom after the central moiety to a terminus:</p> 
24.	The cationic lipid of claim 18, wherein, in at least one hydrophobic tail, the number of carbon atoms between the central moiety and the biodegradable group in the hydrophobic tail ranges from 5 to 10.	<p>For SM-102, the number of carbon atoms between the central moiety and the biodegradable group ranges from 5 to 10.</p> 

25.	The cationic lipid of claim 18, wherein, in at least one hydrophobic tail, the total number of carbon atoms between the central moiety and a terminus of the hydrophobic tail ranges from 15 to 20.	<p>For SM-102, the total number of carbon atoms between the central moiety and a terminus of a hydrophobic tail ranges from 15 to 20:</p> 
26.	The cationic lipid of claim 18, wherein in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by from 8 to 12 carbon atoms.	<p>For SM-102, a terminus is separated from the biodegradable group by from 8 to 12 carbon atoms for the top hydrophobic tail and by from 8 to 12 carbon atoms for the bottom hydrophobic tail.</p> 

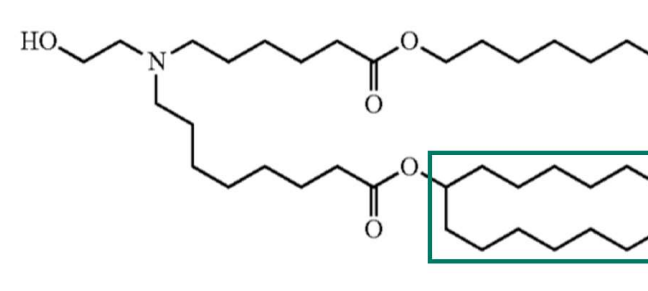
27.	<p>The cationic lipid of claim 26, wherein in at least one hydrophobic tail, the biodegradable group is separated from a terminus of the hydrophobic tail by 8 carbon atoms.</p>	<p>For SM-102, a terminus is separated from the biodegradable group by 8 carbon atoms for a hydrophobic tail.</p>  <p>The chemical structure shows a cationic lipid with a central nitrogen atom. The nitrogen is connected to a hydroxyl group (HO-), a 12-carbon chain, and a 10-carbon chain. The 12-carbon chain is connected to a carbonyl group (C=O) which is linked to an oxygen atom (O-). The 10-carbon chain is connected to a carbonyl group (C=O) which is linked to an oxygen atom (O-). The oxygen atom is connected to a 12-carbon chain. A green box highlights the 8-carbon segment of the 12-carbon chain, indicating the biodegradable group.</p>
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EXHIBIT 3

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
 Washington, DC 20549
FORM 10-K

(Mark One)

- ☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
 For the fiscal year ended December 31, 2021
- OR**
- ☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
 For the transition period from _ to _
 Commission File Number: 001-38753



Moderna, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware

(State or Other Jurisdiction of
Incorporation or Organization)

81-3467528

(IRS Employer Identification No.)

**200 Technology Square
Cambridge, Massachusetts**

(Address of Principal Executive Offices)

02139

(Zip Code)

(617) 714-6500

(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

<u>Title of each class</u>	<u>Trading Symbol(s)</u>	<u>Name of each exchange on which registered</u>
Common stock, par value \$0.0001 per share	MRNA	The Nasdaq Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. **Yes** ☒ **No** ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. **Yes** ☐ **No** ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. **Yes** ☒ **No** ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). **Yes** ☒ **No** ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ Smaller reporting company ☐
 Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. **Yes** ☒ **No** ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). **Yes** ☐ **No** ☒

As of June 30, 2021, the aggregate market value of voting and non-voting common equity held by non-affiliates of the registrant was approximately \$80.8 billion based on the closing sale price on that date of \$234.98. Shares of common stock held by each executive officer and director and by each other person who may be deemed to be an affiliate of the Registrant have been excluded from this computation. The determination of affiliate status for this purpose is not necessarily a conclusive determination for other purposes.

As of February 18, 2022, there were 402,872,986 shares of the registrant's common stock, par value \$0.0001 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement relating to its 2022 Annual Meeting of Stockholders to be filed hereafter are incorporated by reference into Part III of this

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SUMMARY OF THE MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties that you should be aware of before making an investment decision, including those highlighted in the section entitled “Risk Factors.” These risks include, but are not limited to, the following:

- We may encounter difficulties producing, shipping or successfully commercializing our COVID-19 vaccine consistent with our existing or potential contractual obligations, including due to delays or difficulties experienced by our commercial partners;
 - The pharmaceutical market is intensely competitive. We may be unsuccessful in competing effectively in the market for existing products, new treatment methods, and new technologies, including for COVID-19 vaccines;
 - We may be delayed or prevented from receiving full regulatory approval of our COVID-19 vaccine in certain jurisdictions or for certain demographics;
 - We may be unsuccessful in developing future versions of our COVID-19 vaccine to protect against variants of the SARS-CoV-2 virus, or booster doses of our vaccine may not protect against such variants, and a market for vaccines and boosters against these variants may not develop;
 - Preclinical development is lengthy and uncertain, especially for a new class of medicines such as mRNA, and therefore our preclinical programs or development candidates may be delayed, terminated, or may never advance to the clinic, any of which may have a material adverse impact on our platform or our business;
 - Clinical development is lengthy and uncertain, especially with a new class of medicines such as mRNA medicines. Clinical trials of our investigational medicines may be delayed and certain programs may never advance in the clinic or may be more costly to conduct than we anticipate, any of which could have a material adverse impact on our platform or our business;
 - mRNA drug development has substantial clinical development and regulatory risks due to the novel nature of this new class of medicines, and the negative perception of the efficacy, safety, or tolerability profile of any investigational medicines that we or others develop could adversely affect our ability to conduct our business, advance our investigational medicines, or obtain regulatory approvals;
 - Our mRNA products, including our COVID-19 vaccine, development candidates and investigational medicines are based on novel technologies and are complex and difficult to manufacture. We or our third-party manufacturers may encounter difficulties in manufacturing, product release, shelf life, testing, storage, supply chain management, or shipping for any of our medicines;
 - As our drug development pipeline increases and matures, the increased demand for clinical and commercial supplies from our facilities and third parties may impact our ability to operate. We rely on many service providers, all of whom have inherent risks in their operations that may adversely impact our operations;
 - We are subject to significant regulatory oversight with respect to manufacturing our COVID-19 vaccine and our mRNA investigational medicines. Our manufacturing facilities or the manufacturing facilities of our third-party manufacturers or suppliers may not meet regulatory requirements. Failure to meet cGMP requirements set forth in regulations promulgated by the FDA, EMA, and other global health authorities could result in significant delays in any approval of and costs of our products;
 - We have in the past entered into, and in the future may enter into, strategic alliances with third parties for the development and commercialization of our and their products, development candidates and investigational medicines. If these strategic alliances are not successful, our business could be adversely affected;
 - We may seek to establish additional strategic alliances and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans. Certain of our strategic alliance agreements may restrict our ability to develop certain products;
 - If we are not able to obtain and enforce patent protection for our discoveries, or protect the confidentiality of our trade secrets, our ability to effectively compete using our development candidates will be harmed;
 - Our reliance on government funding and collaboration from governmental and quasi-governmental entities for certain of our programs adds uncertainty to our research and development efforts with respect to those programs and may impose requirements that increase the costs of development, commercialization and production of any programs developed under those government-funded programs;
 - We have limited sales, distribution, and marketing experience, and have only recently invested significant financial and management resources to establish these capabilities. If we cannot effectively establish such capabilities or enter into agreements with third parties to market and sell our products or to help ensure compliance with local regulatory requirements, our ability to generate revenues may be adversely affected;
 - Certain of our customers for our COVID-19 vaccine prepay us for a portion of the product payment for the vaccine doses that they expect to receive from us, and under the terms of certain of our supply agreements, we may be required to refund some or all of those prepayments if a customer reduces its purchase commitment or if we fail to deliver the purchased volume;
 - We have a limited history of recognizing revenue from product sales and may not be able to achieve or maintain long-term sustainable profitability;
-

- We may encounter difficulties in managing the development and expansion of our company, which could disrupt our operations;
- Our internal computer systems and physical premises, or those of third parties with which we share sensitive data or information, may fail or suffer security breaches, which could materially disrupt our product development programs and manufacturing operations;
- We are subject to various and evolving laws and regulations governing the privacy and security of personal data, and our failure to comply could adversely affect our business, result in fines and/or criminal penalties, and damage our reputation;
- The price of our common stock has been volatile and fluctuates substantially, which could result in substantial losses for stockholders; and
- Unfavorable U.S. or global economic conditions could adversely affect our business, financial condition, or results of operations.

You should consider carefully the risks and uncertainties described below, in the section entitled “Risk Factors” and the other information contained in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes, before you decide whether to purchase our common stock. The risks described above are not the only risks that we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, including the sections entitled “Business,” “Risk Factors,” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” contains express or implied forward-looking statements within the meaning of the federal securities laws, Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- our activities with respect to our COVID-19 vaccine, and our plans and expectations regarding future generations of our COVID-19 vaccine that we may develop in response to variants of the SARS-CoV-2 virus, ongoing clinical development, manufacturing and supply, pricing, commercialization, if approved, regulatory matters and third-party and governmental arrangements and potential arrangements;
 - our ability to contract with third-party suppliers, distributors and manufacturers and their ability to perform adequately, particularly with respect to the timely production and delivery of our COVID-19 vaccine, including any variant booster vaccine candidates, if authorized;
 - our ability and the ability of third parties with whom we contract to successfully manufacture our commercial products at scale, as well as drug substances, delivery vehicles, development candidates, and investigational medicines for preclinical and clinical use;
 - the scope of protection we are able to establish and maintain for intellectual property rights covering our commercial products, investigational medicines and technology;
 - the initiation, timing, progress, results, and cost of our research and development programs and our current and future preclinical studies and clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our research and development programs;
 - risks related to the direct or indirect impact of the COVID-19 pandemic or any future large-scale adverse health event, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses, initiation or continuation of treatment for diseases that may be addressed by our development candidates and investigational medicines, or in patient enrollment in clinical trials, potential clinical trials, regulatory review or supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 pandemic or future large-scale adverse health event;
 - our anticipated next steps for our development candidates and investigational medicines that may be slowed down due to the impact of the COVID-19 pandemic, including our resources being significantly diverted towards our COVID-19 vaccine efforts, particularly if the federal government seeks to require us to divert such resources;
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- our ability to identify research priorities and apply a risk-mitigated strategy to efficiently discover and develop development candidates and investigational medicines, including by applying learnings from one program to our other programs and from one modality to our other modalities;
- our ability to obtain and maintain regulatory approval of our investigational medicines;
- our ability to commercialize our products, if approved;
- the pricing and reimbursement of our medicines, if approved;
- the implementation of our business model, and strategic plans for our business, investigational medicines, and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our investigational medicines and technology;
- estimates of our future expenses, revenues, capital requirements, and our needs for additional financing;
- the potential benefits of strategic collaboration agreements, our ability to enter into strategic collaborations or arrangements, and our ability to attract collaborators with development, regulatory, and commercialization expertise;
- future agreements with third parties in connection with the commercialization of our investigational medicines, if approved;
- the size and growth potential of the markets for our investigational medicines, and our ability to serve those markets;
- our financial performance;
- the rate and degree of market acceptance of our investigational medicines;
- legal and regulatory developments in the United States and foreign countries;
- our ability to produce our products or investigational medicines with advantages in turnaround times or manufacturing cost;
- the success of competing therapies that are or may become available;
- our ability to attract and retain key scientific or management personnel; and
- developments relating to our competitors and our industry.

In some cases, forward-looking statements can be identified by terminology such as “may,” “should,” “expects,” “intends,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these identifying words. Forward-looking statements are based on our management’s belief and assumptions and on information currently available to our management. Although we believe that the expectations reflected in these forward-looking statements are reasonable, these statements relate to future events or our future operational or financial performance, and involve known and unknown risks, uncertainties, and other factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by these forward-looking statements. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on forward-looking statements. Factors that may cause actual results or events to differ materially from current expectations include, among other things, those listed under the section entitled “Risk Factors” and elsewhere in this Annual Report on Form 10-K. If one or more of these risks or uncertainties occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those expressed or implied by the forward-looking statements. No forward-looking statement is a guarantee of future performance.

The forward-looking statements in this Annual Report on Form 10-K represent our views as of the date of this Annual Report on Form 10-K. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should therefore not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this Annual Report on Form 10-K.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys, and studies conducted by third parties. Industry publications and third-party research, surveys, and studies

generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. We have not independently verified the information contained in such sources.

NOTE REGARDING COMPANY REFERENCES

Unless the context otherwise requires, the terms “Moderna,” the “Company,” “we,” “us,” and “our” in this Annual Report on Form 10-K refer to Moderna, Inc. and its consolidated subsidiaries.

TRADEMARKS

This Annual Report on Form 10-K contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to, including logos, artwork and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies’ trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

PART I**Item 1. Business**

Moderna is pioneering a new class of medicines made of messenger RNA, or mRNA. The potential implications of using mRNA as a drug are significant and far-reaching and could meaningfully improve how medicines are discovered, developed, manufactured and administered.

Since our founding in 2010, we have transformed from a research-stage company advancing programs in the field of mRNA to a commercial enterprise with a diverse clinical portfolio of vaccines and therapeutics across seven modalities, a broad intellectual property portfolio in areas including mRNA and lipid nanoparticle (LNP) formulation, and an integrated manufacturing plant that allows for rapid clinical and commercial production at scale. Moderna has established relationships with a broad range of domestic and overseas government and commercial collaborators, which has allowed for the pursuit of both groundbreaking science and rapid scaling of our manufacturing capabilities. Most recently, Moderna's capabilities have come together to allow the authorization and approval of one of the earliest and most-effective vaccines against the COVID-19 pandemic.

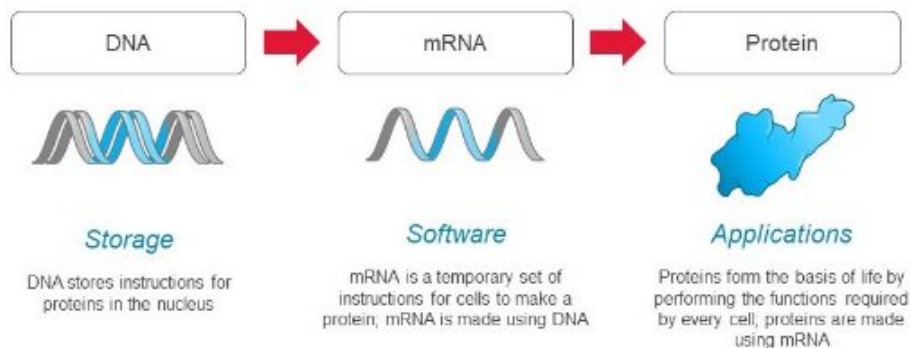
In 2020, mRNA technology emerged as a new class of medicine. In under a year, we designed our vaccine against COVID-19 (mRNA-1273) using mRNA-based technology, conducted clinical trials, which demonstrated that the vaccine was highly effective at preventing COVID-19, and obtained an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) and authorizations from other regulators around the world. During 2021, we shipped more than 800 million doses of our COVID-19 vaccine to countries around the globe to help fight the pandemic, with approximately 25% of those doses going to low- and middle-income countries. In January 2022, the FDA approved the Biologics License Application (BLA) for our COVID-19 vaccine, Spikevax[®], for individuals 18 years of age and older in the United States.

THE mRNA OPPORTUNITY**mRNA, the software of life**

mRNA transfers the information stored in our genes to the cellular machinery that makes all the proteins required for life. Our genes are stored as sequences of DNA which contain the instructions to make specific proteins. DNA serves as a hard drive, safely storing these instructions in the nucleus until they are needed by the cell.

When a cell needs to produce a protein, the instructions to make that protein are copied from the DNA to mRNA, which serves as the template for protein production. Each mRNA molecule contains the instructions to produce a specific protein with a distinct function in the body. mRNA transmits those instructions to cellular machinery, called ribosomes, that make copies of the required protein.

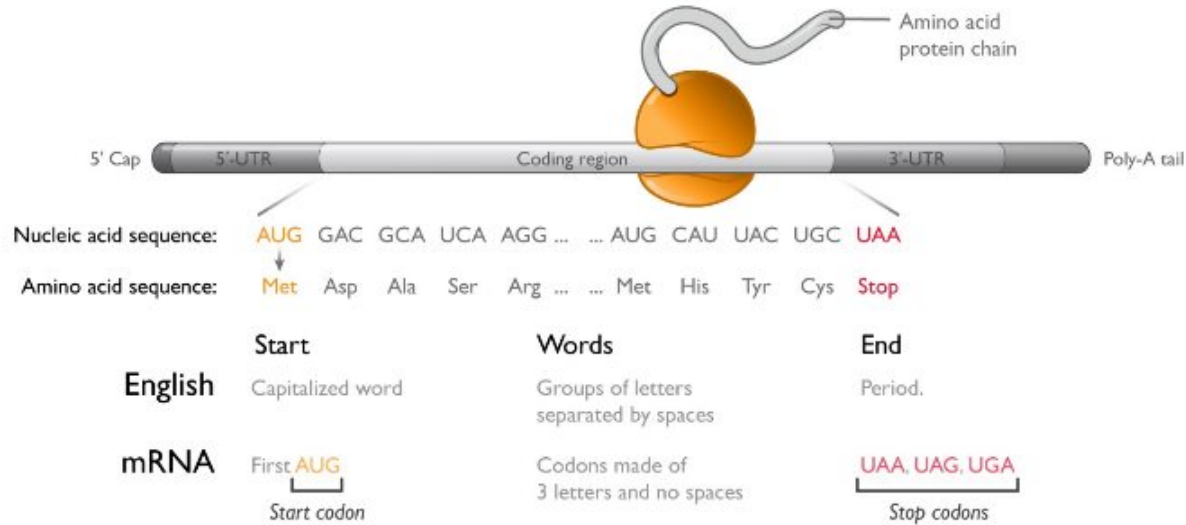
We see mRNA functioning as the “software of life.” Every cell uses mRNA to provide real time instructions to make the proteins necessary to drive all aspects of biology, including in human health and disease. This was codified as the central dogma of molecular biology over 50 years ago, and is exemplified in the schematic below.

**The structure of mRNA**

Messenger RNA is a linear polymer comprising four monomers called nucleotides: adenosine (A), guanosine (G), cytosine (C), and uridine (U). Within the region of the molecule that codes for a protein, or the coding region, the sequence of these four nucleotides forms a language made up of three-letter words called codons. The first codon, or start codon (AUG), signals where the ribosome should start protein synthesis. To know what protein to make, the ribosome then progresses along the mRNA one codon at a time, appending the appropriate amino acid to the growing protein. To end protein synthesis, three different codons (UAA, UAG, and UGA)

serve as stop signals, telling the ribosome where to terminate protein synthesis. In total, there are 64 potential codons, but only 20 amino acids that are used to build proteins; therefore, multiple codons can encode for the same amino acid.

The process of protein production is called translation because the ribosome is reading in one language (a sequence of codons) and outputting in another language (a sequence of amino acids). The coding region is analogous to a sentence in English. Much like a start codon, a capitalized word can indicate the start of a sentence. Codons within the coding region resemble groups of letters representing words. The end of the sentence is signaled by a period in English, or a stop codon for mRNA.



In every cell, hundreds of thousands of mRNAs make hundreds of millions of proteins every day. A typical protein contains 200-600 amino acids; therefore, a typical mRNA coding region ranges from 600-1,800 nucleotides. In addition to the coding region, mRNAs contain four other key features: (1) the 5' untranslated region or 5'-UTR; (2) the 3' untranslated region or 3'-UTR; (3) the 5' cap; and (4) a 3' polyadenosine, or poly-A, tail. The sequence of nucleotides in the 5'-UTR influences how efficiently the ribosome initiates protein synthesis, whereas the sequence of nucleotides in the 3'-UTR contains information about which cell types should translate that mRNA and how long the mRNA should last. The 5' cap and 3' poly-A tail enhance ribosome engagement and protect the mRNA from attack by intracellular enzymes that digest mRNA from its ends.

The intrinsic advantages of using mRNA as a medicine

mRNA possesses inherent characteristics that we believe provide it with a strong foundation as a new class of medicines. These characteristics include:

- **mRNA is used by every cell to produce all proteins:** mRNA is used to make every type of protein, including secreted, membrane, and intracellular proteins, in varying quantities over time, in different locations, and in various combinations. Given the universal role of mRNA in protein production, we believe that mRNA medicines could have broad applicability across human disease.
- **Making proteins inside one's own cells mimics human biology:** Using a person's own cells to produce protein therapeutics or vaccine antigens provides certain advantages over existing technologies such as recombinant proteins, which are manufactured using processes that are foreign to the human body.
- **mRNA has a simple and flexible chemical structure:** Each mRNA molecule comprises four chemically similar nucleotides to encode proteins made from up to 20 chemically different amino acids. To make the full diversity of possible proteins, only simple sequence changes are required in mRNA.
- **mRNA has classic pharmacologic features:** mRNA possesses many of the attractive pharmacologic features of most modern medicines, including reproducible activity, predictable potency, and well-behaved dose dependency; mRNA also provides the ability to adjust dosing based on an individual patient's needs, including stopping or lowering the dose, to seek to ensure safety and tolerability.

mRNA as a new class of medicines

Unlike traditional approaches to medicine, where a protein or chemical is introduced to the body, we send tailored mRNA into cells to instruct them to produce specific proteins. Instead of starting from scratch for each new vaccine or therapy, our mRNA approach

leverages the technology and fundamental components that we have been researching and developing since our founding. Our success in developing, manufacturing and commercializing the Moderna COVID-19 vaccine further supports our belief that mRNA-based medicines as a class have the potential to help patients in far-reaching ways that could exceed the impact of traditional approaches to medicine.

We have developed four core beliefs about the value drivers of mRNA as a new class of medicines:

1. **mRNA has the potential to create an unprecedented abundance and diversity of medicines.** mRNA's breadth of applicability has the potential to create an extraordinary number of new mRNA-based medicines that are currently beyond the reach of recombinant protein technology.
2. **Advances in the development of our mRNA medicines reduce risks across our portfolio.** mRNA medicines share fundamental features that can be used to learn quickly across a portfolio. We believe that once safety and proof of protein production has been established in one program, the technology and biology risks of related programs that use similar mRNA technologies, delivery technologies, and manufacturing processes will decrease significantly.
3. **mRNA technology can accelerate discovery and development.** The software-like features of mRNA enable rapid *in silico* design and the use of automated high-throughput synthesis processes that permit discovery to proceed in parallel rather than sequentially. We believe these mRNA features can also accelerate drug development by allowing the use of shared manufacturing processes and infrastructure.
4. **The ability to leverage shared processes and infrastructure can drive significant capital efficiency over time.** We believe the manufacturing requirements of different mRNA medicines are similar and that at commercial scale, a portfolio of mRNA medicines will benefit from shared capital expenditures.

OUR STRATEGY

We believe that the development of mRNA as a new class of medicines, as evidenced by the development of mRNA-based vaccines during 2020, represents a significant breakthrough for patients and our industry. Our success in developing a highly effective vaccine against COVID-19, going from sequence selection, conducting clinical trials and to receipt of regulatory authorization for emergency use, all in less than a year, provides a visible example of the promise of mRNA-based medicine. The Moderna COVID-19 Vaccine/Spikevax has been authorized for use or approved in over 70 countries. In January 2022, the FDA approved the BLA for Spikevax for individuals 18 years of age and older in the United States. From the beginning of the pandemic through December 31, 2021, we delivered 824 million doses of our vaccine, helping to vaccinate millions of people worldwide and combat the pandemic. We believe our success in developing this vaccine has positive implications beyond infectious disease vaccines and across our entire pipeline. We currently have 44 programs in development, and our pipeline spans five therapeutic areas: infectious diseases, immuno-oncology, rare diseases, cardiovascular diseases and autoimmune diseases.

In order to deliver on the full scope of the mRNA opportunity and maximize long-term value for patients and investors, we have developed four pillars underlying our product strategy that guide our near-term and long-term goals:

1. **Continue to advance our COVID-19 program and bring to market a pan-respiratory annual booster vaccine.** Our long-term vision is to develop, and seek regulatory approval for, a convenient, annual, single-dose booster against as many respiratory viruses as possible. mRNA vaccines have the ability to combine multiple different antigens into one vaccine. We believe a single-dose booster would provide significant value to patients and healthcare systems, as compliance and convenience would increase and there would be a reduction in vaccine administration costs.

This vision includes a single-dose booster vaccine against COVID-19, seasonal flu and respiratory syncytial virus (RSV). We are developing vaccines against each of these diseases individually, while also pursuing parallel development of combination vaccines. We are committed to bringing COVID-19 booster shots (variant-specific, if needed) to the market until the pandemic is under control. We have announced positive Phase 1 data for both our flu vaccine (mRNA-1010) and RSV vaccine (mRNA-1345). mRNA-1010 is preparing for a Phase 3 trial to start in 2022 and mRNA-1345 has started the Phase 3 portion of a pivotal Phase 2/3 study. We are also exploring agreements with governments around the world to establish local manufacturing capabilities in their countries, which would provide those governments with access to these annual vaccines, as well as future pandemic preparedness capabilities.

2. **Bring to market first-in-class vaccines against latent viruses.** Latent viruses, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV), cause acute infections and significant long-term effects, or sequelae. CMV infection is the leading infectious cause of birth defects in children in the U.S. and is a major driver of immune dysfunction with aging, including cardiovascular diseases, cancer and cognitive impairment. EBV infection is a

major cause of infectious mononucleosis (IM), has been tied to increased risk of developing multiple sclerosis, and is associated with certain lymphoproliferative disorders, higher risk of developing cancer/autoimmune diseases and long-COVID. Untreated HIV infection causes impairment of the immune system, leading to acquired immunodeficiency syndrome (AIDS).

Our CMV vaccine (mRNA-1647) is in an ongoing pivotal Phase 3 study to evaluate the safety and efficacy of mRNA-1647 against primary CMV infection in women ages 16-40 years. Our prophylactic EBV vaccine (mRNA-1189) is in an ongoing Phase 1 study. We have two partnered HIV programs, one that is in an ongoing Phase 1 study (mRNA-1644) and another that is preparing to enter the clinic (mRNA-1547). In February 2022, we announced two new development candidates against herpes simplex virus (HSV) and varicella-zoster virus (VZV). Both of these candidates are in preclinical development.

3. **Bring to market therapeutics based on mRNA-encoded proteins.** We believe that mRNA medicines have the potential to provide patients with any therapeutic protein, including those targeting intracellular or membrane proteins. Across our therapeutics pipeline, we have 15 development programs across four therapeutic areas: oncology, cardiovascular, rare disease and autoimmune diseases.

We have had positive, early signals in clinical studies in oncology, cardiovascular and rare diseases, demonstrating early proof-of-concept. However, we are still waiting to advance these programs through full clinical development and regulatory review, as we have done with our COVID-19 vaccine.

4. **Expand our portfolio through strategic investments that leverage or enhance our platform.** As we advance our existing technologies in mRNA and LNP delivery as well as our biology expertise, we believe we can expand our portfolio through collaborations. This strategy includes bringing forward novel nucleic acid editing capabilities through Moderna Genomics (MGX), which is our effort to expand the use of our platform to create more innovative drugs to help patients through complex gene editing. We are committed to advancing this research responsibly and are working toward identifying the right combinations of technologies that can leverage our platform and lead to further breakthroughs in this area.

In December 2021, we announced a collaboration with Metagenomi, Inc., a genetic medicines company with a versatile portfolio of next-generation gene editing tools, focused on advancing new gene editing systems for *in vivo* human therapeutic applications. In January 2022, we announced a collaboration with Carisma Therapeutics, Inc. to discover, develop and commercialize *in vivo* engineered chimeric antigen receptor monocyte (CAR-M) therapeutics for the treatment of cancer.

The strategic principles that guide our approach are:

- **We seek to discover and develop a large pipeline in parallel.** Our goal is to address or prevent as many human diseases as our technology, talent, capital, and other resources permit. We do so as rapidly as we can, understanding both the urgency for patients and the need to be disciplined in our approach.
- **We undertake sustained, long-term investment in technology creation.** We aim to improve the performance of mRNA medicines in our current modalities, and to unlock new modalities, through investments within basic and applied science.
- **We focus on the pace and scale of our learning.** We seek to accelerate our progress by solving numerous technical problems in parallel rather than in sequence. We make significant investments in digital assets and research infrastructure to accelerate the pace and scale of our learning.
- **We integrate across the most critical parts of our value chain.** mRNA is a complex multicomponent system and we believe it demands integration. We believe that we must be directly engaged in research, drug discovery, drug development, process and analytical development, and manufacturing to accelerate our learning, reduce our risk, and protect our critical know-how.
- **We forward invest in core enabling capabilities and infrastructure.** To execute across a broad pipeline, we need to invest at risk before we have all the answers. Our forward investments focus on areas where lead times are long and where early investments can reduce execution risk and accelerate future progress. We proactively invested in a dedicated manufacturing facility, the Moderna Technology Center (MTC), in Norwood, Massachusetts, to support the anticipated growth of our pipeline, and this early investment greatly facilitated our ability to respond to the COVID-19 pandemic by allowing us to begin production of our vaccine even before we received regulatory authorization for its distribution.

OUR PLATFORM

Overview of our platform

Our mRNA “platform” refers to our accumulated knowledge and capabilities in basic and applied sciences. There are three key components to our platform: mRNA, delivery, and the manufacturing process. Our platform incorporates advances across all three of these areas as we advance our medicines. It is the integration of these components that allows us to make our medicines and we combine different versions of mRNA delivery and process into each of our medicines.

There are common features between groups of medicines, which we call “modalities.” These modalities are the application of our platform – the groupings have common features in mRNA or delivery technology or in the process by which they are made. This strategy allows us to manage risk across development programs as well as to understand, in cases of success, where we can rapidly expand and build on success with similar programs.

The primary goal of our platform is to identify new modalities and to expand the utility of our existing modalities. Programs within a modality often have correlated technology risk, but because they pursue diverse diseases, they often have uncorrelated biology risk. Each time we add a modality and a new medicine to our portfolio, we create a network effect because each incremental program can help us gain additional insight into the other the programs in our pipeline.

We have created seven modalities to date:

- Prophylactic vaccines
- Systemic secreted and cell surface therapeutics
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic intracellular therapeutics
- Inhaled pulmonary therapeutics

Our platform: mRNA science advancements

We continue to invest in both basic and applied research, seeking to advance both the state of our technology and the state of the scientific community’s understanding of mRNA. Examples of advances in mRNA science that combine nucleotide chemistry, sequence engineering, and targeting elements are described below.

mRNA chemistry: Modified nucleotides to mitigate immune system activation: The innate immune system has evolved to protect cells from foreign RNA, such as viral RNA, by inducing inflammation and suppressing mRNA translation once detected. Many cells surveil their environment through sensors called toll-like-receptors (TLRs). These include types that are activated by the presence of double-stranded RNA (TLR3) or uridine containing RNA fragments (TLR7, TLR8). Additionally, all cells have cytosolic double-stranded RNA, sensors, including retinoic acid inducible gene-I (RIG-I) that are sensitive to foreign RNA inside the cell.

The immune and cellular response to mRNA is complex, context specific, and often linked to the sensing of uridine. To minimize undesired immune responses to our potential mRNA medicines, our platform employs chemically-modified uridine nucleotides to minimize recognition by both immune cell sensors such as TLR3/7/8, and broadly-distributed cytosolic receptors such as RIG-I.

mRNA sequence engineering: Maximizing protein expression: mRNA exists transiently in the cytoplasm, during which time it can be translated into thousands of proteins before eventually being degraded. Our platform applies bioinformatic, biochemical, and biological screening capabilities, most of which have been invented internally that aim to optimize the amount of protein produced per mRNA. We have identified proprietary sequences for the 5’-UTR that have been observed to increase the likelihood that a ribosome bound to the 5’-end of the mRNA transcript will find the desired start codon and reliably initiate translation of the coding region. We additionally design the nucleotide sequence of the coding region to maximize its successful translation into protein.

Targeting elements: Enabling tissue-targeted translation: All nucleated cells in the body are capable of translating mRNA, resulting in pharmacologic activity in any cell in which mRNA is delivered and translated. To minimize or prevent potential off-target effects, our platform employs technologies that regulate mRNA translation in select cell types. Cells often contain short RNA sequences, called microRNAs or miRNAs, that bind to mRNA to regulate protein translation at the mRNA level. Different cell types have different concentrations of specific microRNAs, in effect giving cells a microRNA signature. microRNA binding directly to mRNA effectively silences or reduces mRNA translation and promotes mRNA degradation. We design microRNA binding sites into the 3’-UTR of our potential mRNA medicines so that if our mRNA is delivered to cells with such microRNAs, it will be minimally translated and rapidly degraded.

Our platform: Delivery science

Our mRNA can, in specific instances, such as our VEGF therapeutic, be delivered by direct injection to a tissue in a simple saline formulation without LNPs to locally produce small amounts of pharmacologically active protein. However, the blood and interstitial fluids in humans contain significant RNA degrading enzymes that rapidly degrade any extracellular mRNA and prevent broader distribution without LNPs. Additionally, cell membranes tend to act as a significant barrier to entry of large, negatively-charged molecules such as mRNA. We have therefore invested heavily in delivery science and have developed LNP technologies to enable delivery of larger quantities of mRNA to target tissues.

LNPs are generally composed of four components: an amino lipid, a phospholipid, cholesterol, and a pegylated-lipid (PEG-lipid). Each component, as well as the overall composition, or mix of components, contributes to the properties of each LNP system. LNPs containing mRNA injected into the body rapidly bind proteins that can drive uptake of LNPs into cells. Once internalized in endosomes within cells, the LNPs are designed to escape the endosome and release their mRNA cargo into the cell cytoplasm, where the mRNA can be translated to make a protein and have the desired therapeutic effect. Any mRNA and LNP components that do not escape the endosome are typically delivered to lysosomes where they are degraded by the natural process of cellular digestion. Examples of tools we developed by using our platform include proprietary LNP formulations that address the steps of mRNA delivery, including cell uptake, endosomal escape, and subsequent lipid metabolism, and for avoidance of counterproductive interactions with the immune system.

Chemistry: Novel lipid chemistry to potentially improve safety and tolerability: We initially used LNP formulations that were based on known lipid systems, which we refer to as “legacy LNPs.” A recognized limitation of these legacy LNPs is the potential for inflammatory reactions upon single and repeat administration that can impact tolerability and therapeutic index. Our later-developed, proprietary LNP systems are therefore designed to be highly tolerated and minimize any LNP vehicle-related toxicities with repeat administration *in vivo*. The changes we made have included engineering amino lipids to avoid the immune system and to be rapidly biodegradable relative to prior lipids.

Composition: Proprietary LNPs enhance delivery efficiency: Our platform includes extensive in-house expertise in medicinal chemistry, which we have applied to design large libraries of novel lipids. Using these libraries in combination with our discovery biology capabilities, we have conducted high throughput screens for desired LNP properties and believe that we have made fundamental discoveries in preclinical studies about the relationships between structural motifs of lipids and LNP performance for protein expression.

Surface properties: Novel LNP design to avoid immune recognition: We have designed our proprietary LNP systems for sustained pharmacology upon repeat dosing by eliminating or altering features that activate the immune system. These are based on insights into the surface properties of LNPs. Upon repeated dosing, surface features on traditional LNPs such as amino lipids, phospholipids, and PEG-lipids, can be recognized by the immune system, leading to rapid clearance from the bloodstream, a decrease in potency upon repeat dosing, and an increase in inflammation. Based on our insights into these mechanisms, we have engineered our LNP systems to reduce or eliminate undesirable surface features. In preclinical studies in non-human primates for our systemic therapeutic development candidates that use our novel LNP systems, we have been able to repeat dose with negligible or undetectable loss in potency, liver damage, and immune system activation.

Our platform: Manufacturing process science

We invest significantly in manufacturing process science to impart more potent features to our mRNA and LNPs, and to invent the technological capabilities necessary to manufacture our mRNA medicines at scales ranging from micrograms to kilograms, as well as achieve pharmaceutical properties such as solubility and shelf life. We view developing these goals of manufacturing and pharmaceutical properties as appropriate for each program, based on its stage of development.

mRNA manufacturing process: Improving pharmacology: Our platform creates mRNA using a cell-free approach called *in vitro* transcription in which an RNA polymerase enzyme binds to and transcribes a DNA template, adding the nucleotides encoded by the DNA to the growing RNA strand. Following transcription, we employ proprietary purification techniques to ensure that our mRNA is free from undesired synthesis components and impurities that could activate the immune system in an indiscriminate manner. Applying our understanding of the basic science underlying each step in the manufacturing process, we have designed proprietary manufacturing processes to impart desirable pharmacologic features, for example increasing potency in a vaccine.

LNP manufacturing process: Improving pharmacology: Our platform technology includes synthetic processes to produce LNPs. Traditionally LNPs are assembled by dissolving the four molecular components, amino lipid, phospholipid, cholesterol, and PEG-lipid, in ethanol and then mixing this with mRNA in an aqueous buffer. The resulting mixture is then purified to isolate LNPs from impurities. Such impurities include molecular components that have not been incorporated into particles, un-encapsulated mRNA that could activate the immune system, and particles outside of the desired size range. Going beyond optimization of traditional manufacturing processes, we have invested in understanding and measuring the various biochemical and physical interactions during LNP assembly and purification. We have additionally developed state-of-the-art analytical techniques necessary to characterize our LNPs and biological systems to analyze their *in vitro* and *in vivo* performance. With these insights, we have identified manufacturing process parameters that drive LNP performance, for example, the potency in a secreted therapeutic setting. These insights have allowed us to make significant improvements in the efficiency of our processing and the potency of our LNPs.

Manufacturing facilities and scale: One of the key aspects of our mRNA platform is that a single manufacturing facility can be used to manufacture any of our mRNA medicines. In 2016, following positive Phase 1 data, we decided to build our clinical manufacturing site in Norwood, Massachusetts. This facility produces not only mRNA medicines for all of our preclinical experiments and clinical trials, but has also produced millions of doses of our COVID-19 vaccine for commercial use. We have also partnered with Lonza and additional contract manufacturing organizations (CMOs) to scale up our manufacturing capabilities globally in an effort to combat the COVID-19 pandemic. We are currently working with governments in different geographies to build additional manufacturing facilities, with a view toward being able to combat future pandemics.

Demonstrations of our platform

Since our founding in 2010, we have made considerable advancements across our platform. Several examples are described below.

Dose-dependent protein expression in the clinic: We have demonstrated in the clinic the ability to generate consistent dose dependent levels of protein (antibodies) as well as the ability to safely repeat dose. For example, we demonstrated the ability to safely repeat dosing in the Phase 1 study of our Chikungunya Antibody program (mRNA-1944), which demonstrated dose-dependent increases in levels of antibodies against chikungunya.

Reproducible pharmacology, including upon repeated dosing: By combining advances in mRNA, delivery, and manufacturing process science, we have demonstrated in preclinical studies sustained and reproducible pharmacology. An example is seen in a mouse model that recapitulates metabolic defects in propionic acidemia (PA). In this rare disease, a defect in one or both of two different subunits (PCCA and PCCB) of the mitochondrial enzyme propionyl-CoA carboxylase results in accumulation of toxic metabolites such as 2-methylcitrate (2MC). In mice hypomorphic for the PCCA subunit, monthly intravenous (IV) administration of mRNAs encoding PCCA and PCCB formulated in our proprietary LNP (mRNA-3927) resulted in a significant and sustained lowering of 2MC throughout the duration of the 6-month study compared to control (luciferase) mRNA (1 mg/kg, n=6/group).

Decreased immune activation upon repeat dosing in non-human primates: We have observed decreased immune activation which enables repeat dosing in non-human primates. Published data indicates serum concentration of human erythropoietin (hEPO) with repeat dosing of mRNA encoding hEPO in our proprietary LNPs with weekly IV administration at 0.2 mg/kg in non-human primates.

Pharmacologic activity in the target tissue and cell: While some of our modalities, such as systemic secreted therapeutics, can leverage many different cell types to make therapeutic proteins, others such as systemic intracellular therapeutics, may require delivery of our mRNA into specific tissues and cell types, for instance hepatocytes in certain liver metabolic diseases. Combining our proprietary mRNA, delivery, and manufacturing process technologies we have observed on-target pharmacologic activity in hepatocytes in non-human primates. The on-target potency of this approach contrasts with traditional delivery technologies. In published data, we have shown one of our proprietary LNPs with increased hepatocyte transfecting properties result in protein expression in liver hepatocytes in non-human primates (demonstrated with a reporter protein detected by immunohistochemistry at 6 hours after IV infusion at 2 mg/kg). Additionally, this LNP results in extended expression of a secreted reporter protein in non-human primates as compared to one of our other proprietary LNPs after IV delivery at 0.1mg/kg.

Our platform's future: Improving and expanding our modalities

We are committed to sustaining investment in our platform, both in basic science to elucidate new mechanistic insights, and in applied science to discover new technologies that harness these insights. Our platform investments have enabled seven modalities to date, most of which have already led to multiple development candidates and investigational medicines in our pipeline. We believe that sustaining our investment in platform research and development will enable further improvements in the current modalities and will lead to the creation of new modalities, both of which will benefit our clinical pipeline in the years ahead.

OUR MODALITIES

Our approach to developing modalities

Within our platform, we develop technologies that enable the development of mRNA medicines for diverse applications. When we identify technologies that we believe could enable a new group of potential mRNA medicines with shared product features, we call that group a “*modality*.” While the programs within a modality may target diverse diseases, they share similar mRNA technologies, delivery technologies, and manufacturing processes to achieve shared product features. The programs within a modality will also generally share similar pharmacology profiles, including the desired dose response, the expected dosing regimen, the target tissue for protein expression, safety and tolerability goals, as well as pharmaceutical properties.

Illustrating our approach: From our first modality to today

We started with prophylactic vaccines as our first modality because we believed this modality faced lower technical hurdles, relative to other areas. Our early formulations of mRNA tended to stimulate the immune system, which would present a challenge to therapeutics but was a desired feature for vaccines. In addition, many potential prophylactic vaccine antigens are well-characterized, allowing us to reduce biology risk. Lastly, the dosing regimens for vaccines require as few as one or two administrations, and generally involve relatively low doses.

For our first programs in this modality we chose our H10N8 and H7N9 pandemic influenza vaccines, each requiring expression of a single membrane protein. We chose to pursue two programs in separate, but parallel, clinical trials to establish the flexibility of our platform. When both programs met our goals for safety, tolerability, and pharmacology, we accelerated and expanded our vaccine pipeline to include multiple commercially meaningful and increasingly complex vaccines.

These included a combination vaccine, designed to protect against two unrelated respiratory viruses, human metapneumovirus (hMPV) and human parainfluenza 3 (PIV3), and a vaccine that combines six different mRNAs, our CMV vaccine, to express a complex pentameric antigen. We also sought strategic alliances with the Defense Advanced Research Projects Agency (DARPA), the Biomedical Advanced Research Development Authority (BARDA) and Merck & Co. (Merck), to allow us to rapidly expand our pipeline and complement our capabilities with their expertise. This early work in the prophylactic vaccines modality led to the ability to introduce our COVID-19 vaccine during 2020 in response to the ongoing pandemic.

Over time, we have taken on more challenging applications and technological hurdles with each successive modality, but we have also tried to build upon our prior experiences to manage risk. For example, in our cancer vaccines modality, we are now applying our technology to elicit T cell responses to potentially recognize and eradicate cancer as a logical extension of our prophylactic vaccines modality. Having demonstrated local expression of protein in our vaccines, we expanded into local therapeutic applications. For example, in our intra-tumoral immuno-oncology modality, we are seeking to use local expression to drive anti-cancer T cell responses by transforming tumor microenvironments. We can also use local expression to drive regenerative processes as in our Vascular Endothelial Growth Factor A (VEGF-A) program. We expanded into two new modalities that use systemic delivery of mRNA to encode secreted and cell surface or intracellular proteins. Most recently, following a breakthrough in pulmonary delivery stemming from our partnership with Vertex Pharmaceuticals (Vertex), we expanded into the inhaled pulmonary therapeutics modality with our cystic fibrosis (CF) program.

Expanding within our designated core modalities

In 2020, we designated the prophylactic vaccines and systemic secreted and cell surface therapeutics modalities as “core modalities” following positive Phase 1 data from our CMV vaccine and chikungunya antibody program, respectively. We believed that this data reduced the risk of these modalities, and our strategy is to invest in additional development candidates within these modalities.

We believe our portfolio of modalities—each with distinct technological and biological risk profiles—allows us to maximize long-term value for patients and investors. We see our seven current modalities as seven distinct product pipelines that represent different risk profiles and benefit from common infrastructure and a shared platform technology. We believe the high technology correlation within a modality allows us to rapidly accelerate the expansion of the pipeline in that modality based on learnings from the initial programs. We believe the lower technology correlation between modalities allows us to compartmentalize the technology risks. We believe our ongoing investments in our platform will lead to the identification of additional new modalities in the future, and will expand the diversity of our pipeline.

Modality descriptions

We currently have seven modalities, described in more detail below:

- **Prophylactic vaccines:** The goal of any vaccine is to safely pre-expose the immune system to a small quantity of a protein from a pathogen, called an antigen, so that the immune system is prepared to fight the pathogen if exposed in the future, and prevent infection or disease.

We believe mRNA vaccines have several advantages: (1) ability to mimic many aspects of natural viral infections, (2) multiplexing of mRNA for more compelling product profiles, (3) rapid discovery and advancement of mRNA programs into the clinic, and (4) capital efficiency and speed from shared manufacturing processes and infrastructure.

- **Cancer vaccines:** The goal of a cancer vaccine is to safely expose the patient's immune system to tumor related antigens, known as neoantigens, to enable the immune system to elicit a more effective antitumor response. Our cancer vaccines modality is focused on the use of mRNA to express neoantigens found in a particular tumor in order to elicit an immune response via T cells that recognize those neoantigens, and therefore the tumor. These neoantigens can either be unique to a patient or can be related to a driver oncogene found across subsets of patients. Recent breakthroughs in cancer immunotherapy, such as checkpoint inhibitors and chimeric antigen receptor T cell therapies, have demonstrated that powerful antitumor responses can be achieved by activating antigen specific T cells. We believe one approach to improve the efficacy of checkpoint inhibitors is to develop vaccines that increase both the number and antitumor activity of a patient's T cells that recognize tumor neoantigens.

We believe that mRNA technology is an attractive approach for cancer vaccines: (1) mRNA vaccines can deliver multiple neoantigens concatenated in a single mRNA molecule, (2) mRNA encoding for neoantigens is translated and processed by patients' endogenous cellular mechanisms for presentation to the immune system, and (3) mRNA vaccines can be efficiently personalized.

- **Intratumoral immuno-oncology:** The goal of this modality is to treat or cure cancer by transforming the tumor microenvironment to drive anti-cancer T cell responses against tumors. The outlook for any patients with advanced cancer remains poor, especially in tumors that have little immune system engagement (sometimes termed immunologically "cold"). In conjunction with a checkpoint inhibitor, we aim to activate the immune system against these otherwise immunologically cold tumors. Intratumoral administration allows for localized effect of these therapeutics that could be toxic if administered systemically.

We believe our approach to immuno-oncology using mRNA medicines could complement checkpoint inhibitors and has several advantages over recombinant protein-based drugs: (1) mRNA focuses and limits exposure of immune stimulatory proteins, (2) mRNA can produce membrane associated immune stimulatory proteins, (3) multiplexing of mRNA allows access to multiple immune stimulatory pathways, (4) mRNA sequences can be engineered to reduce off-target effects, and (5) local administration of mRNA can create a concentration gradient for encoded proteins.

- **Localized regenerative therapeutics:** The goal of this modality is to develop mRNA medicines to address injured or diseased tissues by locally producing proteins that provide a therapeutic benefit in the targeted tissue. There are multiple applications for tissue regeneration and our initial focus is on cardiovascular diseases.

We believe our approach to localized regenerative therapeutics using mRNA has several advantages over alternative approaches: (1) mRNA can be administered locally to produce the desired protein for an extended duration, (2) local administration of mRNA allows for focused activity, and (3) mRNA allows for dose-dependent and repeated production of the encoded protein.

- **Systemic secreted and cell surface therapeutics:** The goal of this modality is to provide secreted proteins, such as antibodies or enzyme replacement therapies across a wide range of diseases, such as heart failure, infectious diseases, and rare genetic diseases. Our mRNA medicines instruct various cells of the human body to secrete proteins for therapeutic effect. Systemically delivered, secreted and cell surface therapeutics, we believe, would allow us to target areas of biology that cannot be addressed using recombinant proteins.

Our potential advantages in this area include: (1) mRNA can produce hard-to-make or complex secreted proteins, (2) mRNA can produce membrane associated proteins, (3) native post-translational modifications are possible through intracellular protein production using mRNA, (4) mRNA can sustain production of proteins, which can increase exposure to proteins with short half-lives, and (5) mRNA allows for desirable pharmacology in rare genetic diseases currently addressed by enzyme replacement therapies.

- **Systemic intracellular therapeutics:** The goal of this modality is to provide intracellular proteins, such as intracellular enzymes and organelle-specific proteins, as safe, tolerable, and efficacious therapies. Our mRNA medicines aim to increase levels of intracellular proteins to achieve a therapeutic effect in one or more tissues or cell types and our initial focus is on rare genetic diseases. Intracellular therapeutics are not currently addressable with recombinant proteins, which are typically administered systemically and cannot reach inside of the cell.

Our potential advantages in these areas include: (1) using mRNA to encode for intracellular and organelle-specific proteins; mRNA can produce hard-to-make or complex proteins, (2) native post-translational modifications are possible through intracellular protein production using mRNA, (3) mRNA can sustain production of proteins, which can increase exposure to proteins with short half-lives, and (4) mRNA allows for desirable pharmacology in complex metabolic diseases.

- **Inhaled pulmonary therapeutics:** The goal of this modality is to develop mRNA medicines that can be delivered to the lung as safe, tolerable and efficacious therapies. We are developing nebulized LNP formulations that can transfect airway epithelial cells to deliver mRNA into the lungs of patients in order to express proteins coded in the mRNA. We aim to leverage our technology for pulmonary diseases in patients for whom there are no existing effective therapies.

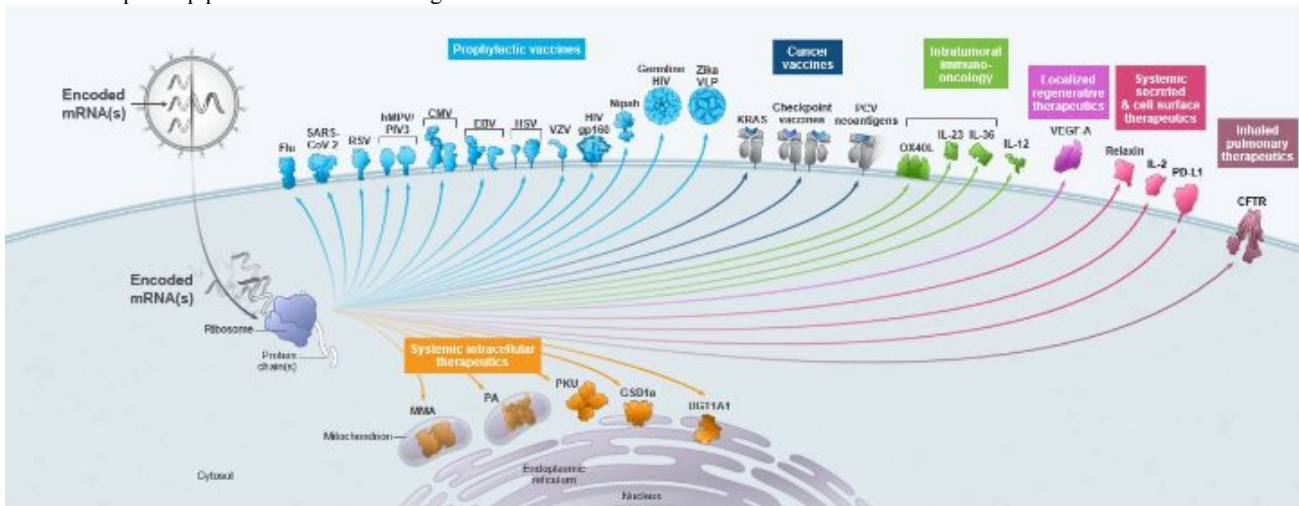
Our potential advantages in these areas include: (1) mRNA can produce hard-to-make or complex proteins, (2) mRNA can replace defective genes, and (3) LNP delivery allows for repeat dosing.

OUR PIPELINE

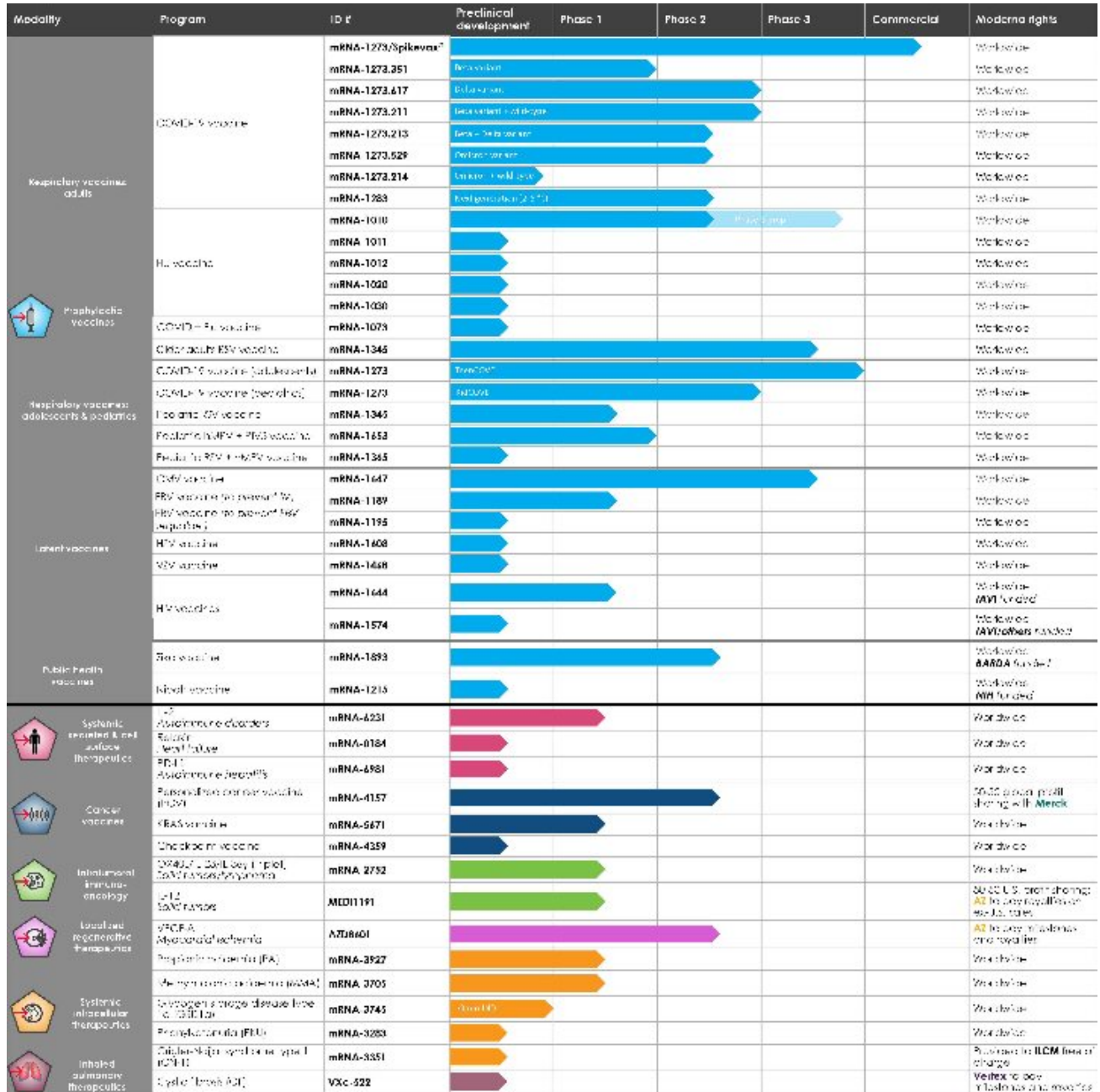
Since we nominated our first program in late 2014, we and our strategic collaborators have advanced in parallel a diverse development pipeline which currently consists of 44 development program across our 41 development candidates, with 25 having entered the clinic and one development candidate subject to an open investigational new drug application (IND). In the third quarter of 2021, we refined the way we track our development programs and now separately track each indication of our COVID-19 and RSV vaccine candidates, which resulted in an increase in the number of our development programs. We have entered seven other development candidates into the clinic that are no longer being pursued for further clinical development. Aspects of our pipeline have been supported through strategic alliances, including with AstraZeneca, Merck, and Vertex, and government-sponsored organizations and private foundations focused on global health initiatives, including BARDA, DARPA, the National Institutes of Health (NIH), and the Bill & Melinda Gates Foundation.

Our selection process for advancing new development candidates reflects both program-specific considerations as well as portfolio-wide considerations. Program-specific criteria include, among other relevant factors, the severity of the unmet medical need, the biology risk of our chosen target or disease, the feasibility of clinical development, the costs of development, and the commercial opportunity. Portfolio-wide considerations include the ability to demonstrate technical success for our platform components within a modality, thereby increasing the probability of success and learnings for subsequent programs in the modality and in some cases in other modalities.

The breadth of biology addressable using mRNA technology is reflected in our current development pipeline of 44 programs. The diversity of proteins made from mRNA within our development pipeline is shown in the figure below.



Our full pipeline, grouped by modalities, is shown in the figure below:



PROPHYLACTIC VACCINES MODALITY

We have 29 different prophylactic vaccine programs, of which 17 have entered the clinic. We separate our prophylactic vaccines modality into three categories: (1) vaccines against respiratory viruses, (2) vaccines against latent viruses, and (3) other vaccines (such as public health programs).

Prophylactic vaccines: Vaccines against respiratory viruses

COVID-19 vaccine (mRNA-1273)

Moderna's COVID-19 Vaccine/Spikevax is approved or authorized for use in more than 70 countries

The Moderna COVID-19 Vaccine, which is also marketed under the brand name Spikevax, is our first commercial product. From the beginning of the COVID-19 pandemic through December 31, 2021, we delivered approximately 824 million doses of our vaccine globally, with approximately 807 million of those doses shipped in 2021.

Coronaviruses are a large family of viruses that can cause illness in animals or humans. In humans there are several known coronaviruses that cause respiratory infections. These coronaviruses range from the common cold to more severe diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. SARS-CoV-2 is the novel coronavirus first identified in humans in December 2019 and is the cause of COVID-19. COVID-19 is the most severe global pandemic since the influenza pandemic of 1918. According to the Johns Hopkins Coronavirus Resource Center, since the identification of SARS-CoV-2 in 2020, there have been over 430 million confirmed cases and over 5.9 million global deaths from COVID-19. The risk of mortality increases with age and the risk of severe disease and mortality increase for persons with pre-existing diseases or comorbid conditions (e.g. cardiovascular disease, diabetes, chronic lung disease, obesity).

Our vaccine against COVID-19, mRNA-1273, was designed, subject to Phase 1, Phase 2 and Phase 3 clinical trials, delivered clinical trial results, and received emergency use and other conditional authorizations in less than a year, and has been and continues to be a key tool in fighting the global COVID-19 pandemic. The SARS-CoV-2 virus continues to evolve, and certain variants of the virus have proven to be more transmissible and to cause more severe cases of COVID-19 than the ancestral strain that first emerged in Wuhan, China. As part of our strategy to combat the COVID-19 pandemic, we have continued to develop and assess variant-specific versions of our COVID-19 vaccine, including versions aimed at targeting the Beta, Delta and Omicron variants of the virus. Forward-looking references to our COVID-19 vaccine in this Annual Report on Form 10-K may include future modifications to mRNA-1273 or other development candidates that are designed to provide protection against variants of the SARS-CoV-2 virus.

We continue to study the use of our COVID-19 vaccine (mRNA-1273) in adolescent and pediatric populations, and for boosting and other indications. In addition to our original COVID-19 vaccine, we have advanced multiple other variant-specific vaccines into the clinic as part of effort to fight the global COVID-19 pandemic. As of the date of this Annual Report on Form 10-K, these programs include:

Spikevax/mRNA-1273 Programs

- Moderna COVID-19 vaccine/Spikevax: Approved/authorized in individuals 18 years and older in more than 70 countries (100 µg dose).
 - In January 2022, the U.S. FDA approved the Biologics License Application (BLA) for Spikevax (COVID-19 Vaccine, mRNA) to prevent COVID-19 in individuals 18 years of age and older.
- Adolescent COVID-19 vaccine/Spikevax: Authorized in individuals 12-17 years in the European Union, UK, Australia, Canada, Switzerland and other countries (100 µg dose); authorization by the U.S. FDA is pending.
 - The U.S. FDA notified us that it will require additional time to complete its assessment of our EUA request for the use of mRNA-1273 at the 100 µg dose level in adolescents 12 to 17 years of age. In early December 2021, we also decided to evaluate the potential of a lower 50 µg dose for primary vaccination.
- Pediatric COVID-19 vaccine/Spikevax: In clinical trials in children from 6 months to 11 years old; authorized in individuals 6-11 years in Australia, and subject to a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use in individuals from 6-11 years (50 µg dose).
 - The Phase 2 study of mRNA-1273 in pediatric populations is ongoing. We selected the 50 µg dose for expanded enrollment in the 6 to 11 years old cohort, which is now fully enrolled (N=4,000). Dose selection studies are underway for 2 years to 5 years old and 6 months to <2 years old groups. In early December 2021, we also decided to evaluate the potential of a lower dose of 25 µg to meet regulatory guidance for immunogenicity in children 6-11 years of age. We expect to report data in children 2-5 years of age in March 2022.
- Booster dose of COVID-19 vaccine/Spikevax: Authorized in individuals 18 years and older in the United States, the European Union, Switzerland and other countries (50 µg dose).
 - For immunocompromised individuals, a booster dose of 100 µg is authorized.

Other COVID-19 Vaccine Programs

- Next-generation COVID-19 vaccine (mRNA-1283) is in an ongoing Phase 2 trial.
 - mRNA-1283 is a next-generation COVID-19 vaccine candidate that encodes for the portions of the SARS-CoV-2 spike protein critical for neutralization, specifically the Receptor Binding Domain (RBD) and Nterminal Domain (NTD). The encoded mRNA-1283 antigen is shorter than mRNA-1273 and is being developed as a potential refrigerator-stable mRNA vaccine that will facilitate easier distribution and administration by healthcare providers.
- Variant-specific or multi-valent COVID-19 vaccines: As SARS-CoV-2 has continued to evolve, we have proactively made new mRNA candidates in the case they are needed for an escape variant. In the event that mRNA-1273 proves ineffective at protecting against these variants, we have developed the variant vaccines listed below, which may be utilized to the extent necessary as the virus continues to evolve:
 - mRNA-1273.351: Vaccine against the Beta variant. Phase 2 clinical trial ongoing.
 - mRNA-1273.617: Vaccine against the Delta variant. Phase 2 clinical trial ongoing.
 - mRNA-1273.529: Vaccine against the Omicron variant. Phase 2 clinical trial ongoing.
 - mRNA-1273.211: Vaccine against the Beta variant and wild-type. Phase 2 clinical trial ongoing.
 - mRNA-1273.213: Vaccine against the Beta variant and Delta variant. Phase 2 clinical trial ongoing.
 - mRNA-1273.214: Vaccine against the Omicron variant and wild-type.

Moderna COVID-19 Vaccine Clinical Trials

The final analysis of adjudicated cases from the Phase 3 clinical trial for mRNA-1273, which we refer to as the COVE Study, demonstrated efficacy of 93% through six months after the second dose of the vaccine. The final analysis also demonstrated greater than 98% efficacy against severe cases of COVID-19 and 100% efficacy against death caused by COVID-19 in the per protocol cohort. The final analysis also demonstrated consistency in our subgroup analysis, including analyses by gender, by race and by preexisting medical conditions. The safety profile for mRNA-1273 continues to be consistent with the Phase 3 data over the longer period of safety follow up and across population subgroups.

Variant-specific and multivalent vaccines and Omicron update

We are continuously advancing booster candidates to address emerging variants of concern (VOCs). The strategy involves evaluating the prototype vaccine (mRNA-1273) at the authorized booster dose (50 µg), an Omicron-specific booster candidate (mRNA-1273.529), and a bivalent booster candidate (mRNA-1273.214) combining mRNA-1273.529 and mRNA-1273. Booster candidates are being evaluated in ongoing Phase 2/3 studies of approximately 300-600 participants per arm. In December 2021, we announced that at day 29 post-boost, the authorized 50 µg booster of mRNA-1273 increased neutralizing geometric mean titers (GMT) against Omicron approximately 37-fold higher than pre-boost levels. At day 29 post-boost, the 100 µg dose booster of mRNA-1273 increased neutralizing GMTs approximately 83-fold higher than pre-boost levels. Multivalent candidates (mRNA-1273.211 and mRNA-1273.213) boosted Omicron specific neutralizing antibody levels to similarly high levels at both the 50 µg and 100 µg levels. Based on the strength of neutralizing titers generated by mRNA-1273, the rapid pace of Omicron expansion, and the increased complexity of deploying a new vaccine, we are focusing our near-term efforts to address Omicron on the mRNA-1273 booster.

However, given the long-term threat demonstrated by Omicron's immune escape, we are also developing an Omicron containing variant vaccine (mRNA-1273.529) and a bivalent vaccine that is tailored to Omicron and the wild-type virus (mRNA-1273.214). The first participant was dosed in the mRNA-1273.529 trial in January 2022 and this trial is ongoing.

COVID-19 Commercial, Manufacturing and Supply Updates

Commercial sales of our COVID-19 vaccine accounted for \$17.7 billion in revenues for the year ended December 31, 2021, based upon the delivery of approximately 807 million doses of the vaccine, accounting for all of our commercial revenues. We anticipate that sales of our COVID-19 vaccine in 2022 will similarly provide all of our commercial revenues for the coming year. These sales, both for 2021 and 2022, have been and will primarily be made to governments and international organizations engaged in the purchase of vaccines to combat the COVID-19 pandemic. We are preparing for the fall 2022 booster season and, if marketing approval is received for boosters of our COVID-19 vaccine, we expect to initiate sales in the U.S. private market. As the COVID-19 pandemic evolves into an endemic phase, we anticipate greater seasonality for sales, with greater demand in the fall/winter season in each hemisphere as countries seek to boost their populations. For further information on the sales and manufacturing of our COVID-19 vaccine, see "Manufacturing" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" below.

Seasonal influenza vaccine (mRNA-1010, mRNA-1011, mRNA-1012, mRNA-1020 and mRNA-1030)

We are developing five influenza vaccines. mRNA-1010 has reported positive Phase 1 data and is ongoing in a Phase 2 study and a Phase 3 study is planned to start soon.

Seasonal influenza viruses are estimated by the World Health Organization (WHO) to cause 3 to 5 million cases of severe illness and up to 650,000 deaths each year, resulting in a severe challenge to public health. Currently licensed seasonal influenza virus vaccines rarely exceed 60% overall effectiveness and can provide low effectiveness during years when the circulating viruses do not match the strains selected for the vaccine antigens. Our mRNA seasonal influenza vaccine program has three different approaches. Our first approach – Quadrivalent Vaccine – is developing a quadrivalent seasonal flu vaccine (mRNA-1010) targeting WHO recommendations, including A H1N1, H3N2 and influenza B Yamagata and Victoria lineages. Our second approach – Expanded Coverage – is to provide an enhanced antigen selection opportunity to public health authorities with the potential for regional variation. Our third approach – Immunologic Breadth – is to provide immunity by targeting more conserved antigens to provide the broadest coverage. We also aim to work with the WHO and other regulators to make vaccines closer to the flu season and potentially choose strains closer to the ones circulating in the hemisphere.

mRNA-1010 is a single investigational vaccine consisting of four distinct mRNA sequences that encode the A H1N1, H3N2 and influenza B Yamagata and Victoria lineages in our proprietary LNP. mRNA-1011 and mRNA-1012 are investigational vaccines that will include the four WHO recommended strains and aim to add additional Hemagglutinin (HA) antigens (e.g. H3N2, H1N1). mRNA-1020 and mRNA-1030 are investigational vaccines that will aim to add Neuraminidase (NA) antigens.

Latest data and next steps

mRNA-1010 is ongoing in a Phase 2 study and a Phase 3 efficacy study is planned to start in 2022. In December 2021, we announced positive Phase 1 data, and that mRNA-1010 successfully boosted hemagglutination inhibition (HAI) assay geometric mean titers against all strains 29 days after vaccination at all doses tested in both younger and older adults. In the Phase 1 study, mRNA-1010 was evaluated at 50 µg, 100 µg and 200 µg dose levels in younger adult (age 18-49) and older adult (age 50+) cohorts. No significant safety findings were observed through day 29. Adverse reactions (ARs) were generally reported more frequently in younger adults compared to older adults, and at higher dose levels. Minimal differences in dose response was observed between the 50 µg, 100 µg and 200 µg dose levels, suggesting the potential to explore even lower doses.

Our expanded coverage influenza vaccines (mRNA-1011 & mRNA-1012) and immunologic breadth influenza vaccines (mRNA-1020 & mRNA-1030) are in preclinical studies.

RSV vaccine (mRNA-1345)

We are developing an RSV vaccine for children and older adults. In older adults, mRNA-1345 is ongoing in a pivotal Phase 3 study; in pediatrics, mRNA-1345 is ongoing in a Phase 1 study.

Respiratory syncytial virus (RSV) is one of the most common causes of respiratory disease in children under the age of five and also in older adults. Most children are infected at least once by two years of age. In the United States, it is estimated that over two million children younger than five years of age receive medical attention and more than 86,000 are hospitalized due to RSV infection annually. RSV also causes a substantial burden of respiratory illness in older adults. RSV infection causes an estimated 177,00 hospitalizations and 14,000 deaths per year in adults aged >65 years in the United States.

mRNA-1345 encodes an engineered form of the RSV F protein stabilized in the prefusion conformation and is formulated in our proprietary LNP. We believe that neutralizing antibodies elicited by mRNA-1345 may lead to an efficacious RSV vaccine.

Latest data and next steps

The Phase 1 study of mRNA-1345 to evaluate the tolerability, reactogenicity and immunogenicity of mRNA-1345 in younger adults, older adults, older adults of Japanese descent, women of child-bearing age and children with serologic evidence of prior RSV exposure is ongoing. The age range of children in this de-escalation Phase 1 study is 12-59 months. Enrollment in the pediatric and older adult Japanese descent cohorts are ongoing, whereas the other cohorts are fully enrolled. Phase 1 interim data from the older adult cohort showed that a single mRNA-1345 vaccination at 50 µg, 100 µg or 200 µg boosted neutralizing antibody titers against RSV-A by approximately 14-fold and against RSV-B by approximately 10-fold.

The Phase 3 portion of the pivotal global Phase 2/3 study of mRNA-1345 with approximately 34,000 participants and testing the 50 µg is currently enrolling. The FDA has granted Fast Track designation for mRNA-1345 in adults older than 60 years of age.

hMPV/PIV3 vaccine (mRNA-1653)

We are developing a combination vaccine to address two viruses that are leading causes of respiratory infection

Human metapneumovirus (hMPV) and human parainfluenza virus 3 (PIV3) are significant causes of respiratory tract infections in children. hMPV has been detected in 4% to 15% of patients with acute respiratory infections. hMPV causes disease primarily in young children but can also infect adults, the elderly, and immunocompromised individuals. Infections from parainfluenza virus (PIV) account for up to 7% of acute respiratory infections among children younger than 5 years. Of the four PIV types identified, PIV3 most frequently results in infections and leads to the more serious lower respiratory tract infections compared to the other three PIV types.

mRNA-1653 is a single investigational vaccine consisting of two distinct mRNA sequences that encode the membrane F proteins of hMPV and PIV3, co-formulated in our proprietary LNP.

Latest data and next steps

A first-in-human dose-ranging study, mRNA-1653-P101, in healthy adults (N=124) was completed in January 2020. This study evaluated the safety, reactogenicity, and immunogenicity of a range of dose levels (25, 75, 150 or 300 µg) administered on a 1-dose or 2-dose vaccination schedule (approximately 28 days apart) compared with a placebo control in healthy adult subjects (18 through 49 years of age) with a 13 month follow-up period. The mRNA-1653 vaccine was generally well-tolerated at all dose levels. A single dose of mRNA-1653 boosted serum neutralization titers against hMPV and PIV3, and the magnitude of the boost was similar at all dose levels. The Month 1 to baseline geometric mean ratio (GMR) for the pooled mRNA-1653 treatment groups was approximately 6 for hMPV and 3 for PIV3. A second vaccination did not impact the magnitude of hMPV or PIV3 neutralization titers measured at Month 2. The hMPV neutralizing antibody titers remained above baseline at all dose levels through Month 13, and the PIV3 neutralizing antibody titers remained above baseline at all dose levels through Month 7.

We are conducting a Phase 1b trial to evaluate mRNA-1653 in healthy adults and children aged 12-59 months. The Phase 1b trial is a randomized, observer-blinded, placebo-controlled, dose-ranging trial to evaluate the safety and immunogenicity of two dose levels of mRNA-1653 in healthy adults (18-49 years of age) and two dose levels in children (12-59 months of age) with serologic evidence of prior hMPV and PIV3 exposure. The study is fully enrolled.

Combination vaccines (mRNA-1073 & mRNA-1365)

Our vision is to develop a pan-respiratory annual booster vaccine (mRNA-1073) and a pediatric combination vaccine (mRNA-1365)

In September 2021, we announced two development candidates that build upon our combination strategy. mRNA-1073 is our COVID-19 and seasonal flu combination vaccine. mRNA-1073 encodes for the COVID-19 spike protein and the flu HA glycoproteins. mRNA-1365 is our pediatric RSV and hMPV combination vaccine. mRNA-1365 encodes for the RSV prefusion F glycoprotein and the hMPV F protein.

Prophylactic vaccines: Vaccines against latent viruses

CMV vaccine (mRNA-1647)

Our CMV program targets prevention of CMV infections, which could reduce the risk of birth defects

Human CMV is a common human pathogen and member of the herpes virus family. Congenital CMV results from infected mothers transmitting the virus to their unborn child and it is the leading infectious cause of birth defects in the United States, with approximately 25,000 newborns in the U.S. infected annually. There is currently no available vaccine for CMV and a vaccine that leads to durable immunity in women of child-bearing age would address a critical unmet need in the prevention of congenital CMV infection.

Our CMV vaccine, mRNA-1647, combines six mRNAs in one vaccine, which encode for two proteins located on the surface of CMV: five mRNAs encoding the subunits that form the membrane-bound pentamer complex and one mRNA encoding the full-length membrane-bound glycoprotein B (gB). Both the pentamer and gB are essential for CMV to infect barrier epithelial surfaces and gain access to the body, which is the first step in CMV infection. mRNA-1647 is designed to produce an immune response against both the pentamer and gB for the prevention of CMV infection.

Latest data and next steps

Phase 1 and 2 studies of mRNA-1647 demonstrated functional antigen-specific responses that support the vaccine candidate's potential to prevent CMV infection. Interim, seven-month data from the Phase 2 study of mRNA-1647 at the 50 µg, 100 µg and 150 µg dose levels showed that mRNA-1647 was generally well tolerated. In CMV-seronegative participants in mRNA-1647 treatment groups after the third vaccination, neutralizing antibody GMTs against epithelial cell infection were at least 20-fold higher than the baseline GMT of the CMV seropositive group, and neutralizing antibody GMTs against fibroblast infection approximated the baseline

GMT of the CMV-seropositive group. In CMV positive participants in mRNA-1647 treatment groups after the third vaccination, neutralizing antibody GMTs against epithelial cell infection increased to at least 6.8-fold over baseline, and neutralizing antibody GMTs against fibroblast infection increased to approximately 2-fold over baseline.

Based on the interim analysis of the Phase 2 study, the 100 µg dose was chosen for the Phase 3 study. The first participant in the Phase 3 study, known as CMVictory, was dosed in October 2021. The study is evaluating the safety and efficacy of mRNA-1647 against primary CMV infection in women ages 16-40 years and seeks to enroll 6,900 women of child-bearing age.

EBV vaccine (mRNA-1189 & mRNA-1195)

We are developing two EBV vaccines – a vaccine to prevent infectious mononucleosis and another vaccine to prevent the longer term sequelae of EBV infection

Epstein-Barr virus (EBV) a member of the herpesvirus family that includes CMV, infects approximately 90% of people by adulthood, with primary infection typically occurring during childhood or late adolescence (approximately 50% and 89% seropositivity, respectively) in the U.S. EBV is the major cause of infectious mononucleosis in the U.S., accounting for over 90% of the approximately 1-2 million cases of infectious mononucleosis in the U.S. each year. Infectious mononucleosis can debilitate patients for weeks to months and, in some cases, can lead to hospitalization and splenic rupture. EBV infection is associated with the development and progression of certain lymphoproliferative disorders, cancers, and autoimmune diseases. In particular, EBV infection and infectious mononucleosis are associated with increased risk of developing multiple sclerosis, an autoimmune disease of the central nervous system.

Similar to our CMV vaccine (mRNA-1647) product concept, we believe that an effective EBV vaccine must generate an immune response to antigens that are required for viral entry in most of the susceptible cell types. We have thus designed our EBV vaccine, mRNA-1189, to elicit an immune response to EBV envelope glycoproteins gp220 as well as gp42, and the gH/gL complex, which are required for infection of both epithelial and B cells. mRNA-1189 contains four mRNAs encoding for these proteins encapsulated in our proprietary LNPs. mRNA-1195 encodes for additional antigens and the first indication it will focus on is post-transplant lymphoproliferative diseases (80% of PTLTD can be attributed to EBV).

Latest data and next steps

We are conducting a Phase 1, randomized, observer-blind, placebo-controlled study of mRNA-1189. The primary purpose of the Phase 1 study is to assess safety, tolerability and immunogenicity of mRNA-1189 in healthy adults ages 18 to 30. We announced the dosing of the first participant in January 2022 and we expect to enroll approximately 270 participants. Our EBV therapeutic vaccine, mRNA-1195, is in preclinical studies.

HSV vaccine (mRNA-1608)

We are developing a herpes simplex virus (HSV) vaccine candidate against HSV-2 disease

Herpes simplex viruses (commonly known as herpes) are categorized into two types: HSV-1 infects the mouth, face and genitals, and HSV-2 primarily infects the genitals. Both viruses establish life-long latent infections within nearby sensory neurons from which they can reactivate and re-infect the skin. There is a significant burden of disease from HSV genital infections. Diagnosed, symptomatic genital herpes causes a reduction in quality of life, which antivirals (current standard of care) only partially restore. In the United States, approximately 18.6 million adults ages 18 to 49 years are living with HSV-2. Globally, approximately 5% of the population in the 18-to-49-year age range is HSV-2 seropositive.

We believe that an HSV vaccine could deliver similar efficacy as suppressive antiviral treatments and could improve compliance and quality of life. We aim to induce a strong antibody response with neutralizing and effector functionality combined with cell-mediated immunity.

Latest data and next steps

Our HSV vaccine (mRNA-1608) is currently in preclinical studies. In a preclinical study in mice, we demonstrated robust neutralizing response induced by an mRNA vaccine containing HSV-2 antigens against both HSV-2 infection, and cross-neutralization against HSV-1 infection. In addition, the sera also demonstrated high antibody-dependent cellular cytotoxicity (ADCC) activity. The immune responses induced by the HSV-2 mRNA vaccine are higher than the average observed in 80 randomly selected seropositive human sera.

VZV vaccine (mRNA-1468)

We are developing a varicella-zoster virus (VZV) vaccine candidate to reduce the rate of herpes zoster (shingles)

Herpes zoster occurs in one of three adults in their lifetime and incidence dramatically increases at approximately 50 years of age. Declining immunity in older adults decreases cell-mediated immunity against VZV, allowing reactivation of the virus from latently infected neurons, causing painful and itchy lesions. Serious herpes zoster complications include postherpetic neuralgia (10-13% of herpes zoster cases), bacterial coinfections, and cranial and peripheral palsies; 1-4% of individuals with herpes zoster cases are hospitalized for complications. Severity of disease and likelihood of complications, including postherpetic neuralgia (PHN) also increases with age. Immunocompromised patients, autoimmune disease patients using immunosuppressive therapies, HIV-infected patients, hematopoietic stem cell (HSCT) and organ transplant recipients have an increased risk of developing herpes zoster. The incidence of herpes zoster has been increasing throughout the world, from 0.76 per 1,000 person years from 1945 to 1949, to 7.2 per 1,000 person years in 2016. The current standard of care is Shingrix™, an FDA-approved vaccine for the prevention of shingles (herpes zoster) in adults 50 years and older. It is more than 90% effective against herpes zoster in adults aged 50-70 with only a slight reduction in efficacy for adults over age 70.

Our VZV vaccine (mRNA-1468) is designed to express VZV glycoprotein E (gE) to reduce the rate of herpes zoster.

Latest data and next steps

In partnership with Merck, we previously published preclinical data in *Vaccine* showing that an LNP formulated (Merck's proprietary LNP) mRNA encoding VZV gE antigen is highly immunogenic in non-human primates. Our VZV vaccine (mRNA-1468) using our proprietary LNP is currently in preclinical studies.

HIV vaccine (mRNA-1644 & mRNA-1574)

We are developing two HIV vaccines – one approach is to test a novel HIV vaccine strategy in humans for eliciting broadly neutralizing HIV-1 antibodies (bnAbs) and the second approach is to test novel HIV trimer designs in humans.

HIV is the virus responsible for acquired immunodeficiency syndrome (AIDS), a lifelong, progressive illness with no effective cure. Approximately 38 million people worldwide are currently living with HIV, with 1.2 million in the U.S. Approximately 1.5 million new infections of HIV are acquired worldwide every year and approximately 680,000 people die annually due to complications from HIV/AIDS. The primary routes of transmission are sexual intercourse and IV drug use, putting young adults at the highest risk of infection. From 2000 to 2015, a total of \$562.6 billion globally was spent on care, treatment and prevention of HIV, representing a significant economic burden.

In collaboration with the International AIDS Vaccine Initiative (IAVI) and the Bill & Melinda Gates Foundation, mRNA-1644 is testing a novel HIV vaccine strategy in humans as delivered by mRNA to elicit broadly neutralizing HIV-1 antibodies (bnAbs) through sequential vaccination of novel prime and boost antigens that induce specific B-cell responses. In collaboration with IAVI and the HIV Vaccine Trials Network, mRNA-1574 is testing multiple native-like HIV trimer mRNAs in humans to improve our understanding of how to make stable and immunogenic native-HIV trimers.

Latest data and next steps

mRNA-1644 is in an ongoing Phase 1 clinical trial and mRNA-1574 is in preclinical studies.

Prophylactic vaccines: Public health vaccines

Zika vaccine (mRNA-1893)

In partnership with BARDA, we are in a Phase 2 clinical trial for our Zika vaccine

The Zika virus is a single stranded RNA virus of the flaviviridae family. Seroepidemiology data suggest that it is endemic to regions of Africa and Asia where the Aedes mosquito vectors are found. Zika virus is predominantly spread by mosquitos from the Aedes genus, but it can also be transmitted congenitally, sexually, and through blood donation. Zika infection is usually asymptomatic or mild in adults, leading to fever, rash, and conjunctivitis. However, infection of women during pregnancy can result in devastating microcephaly in newborns. Microcephaly is a birth defect characterized by an abnormally small head and brain, associated with lifelong neurodevelopmental delay, seizures, intellectual disability, balance problems, and dwarfism / short stature, resulting in significant disability and requiring lifelong support. In 2007, a Zika infection outbreak progressed across the Pacific islands. An outbreak observed in Brazil in 2015 soon spread across the Americas. This led to the WHO declaring it a public health emergency of international concern in 2016. During the period, there were tens of thousands of cases of microcephaly and congenital Zika syndrome reported in infants and of resulting neurological sequelae such as Guillain-Barré syndrome reported in adults.

Our Zika vaccine, mRNA-1893, encodes for the prME structural protein encapsulated in our proprietary LNP.

Latest data and next steps

In 2020, we announced positive data from our Phase 1 clinical trial, which enrolled four cohorts (10, 30, 100 and 250 µg). mRNA-1893 was safe and well tolerated at the 10 and 30 µg dose level. In the flavivirus-seronegative group, seroconversion rates after the second vaccination reached 94.4% at the 10 µg dose level and 100% in the 30 µg dose level (PRNT₅₀). In the flavivirus-seropositive group, the percentage of participants achieving a 4-fold boost in pre-existing PRNT₅₀ titers after the second vaccination reached 50% in the 10 µg dose level and 75% in the 30 µg dose level (PRNT₅₀). We are currently enrolling mRNA-1893 in a Phase 2 clinical study in the United States and Puerto Rico with approximately 800 participants. The randomized, placebo-controlled study aims to evaluate the safety, tolerability and reactogenicity of mRNA-1893 compared to placebo.

Nipah vaccine (mRNA-1215)

In collaboration with the NIH-VRC, we are preparing to start a Phase 1 study for our Nipah vaccine

Nipah virus (NiV) is a zoonotic virus transmitted to humans from animals, contaminated food, or through direct human-to-human transmission and causes a range of illnesses including fatal encephalitis. Severe respiratory and neurologic complications from NiV have no treatment other than intensive supportive care. The case fatality rate among those infected is estimated at 40-75%. NiV outbreaks cause significant economic burden to impacted regions due to loss of human life and interventions to prevent further spread, such as the slaughter of infected animals. NiV has been identified as the cause of isolated outbreaks in India, Bangladesh, Malaysia, and Singapore since 2000 and is included on the WHO R&D Blueprint list of epidemic threats needing urgent R&D action.

Latest data and next steps

mRNA-1215, our vaccine candidate against the Nipah virus (NiV), was co-developed along with the NIH's Vaccine Research Center. The Phase 1 clinical testing will be focused on pandemic preparedness.

SYSTEMIC SECRETED AND CELL SURFACE THERAPEUTICS MODALITY

Our systemic secreted and cell surface therapeutics modality currently has three active development programs, of which one has entered the clinic. We previously announced positive data from our Chikungunya Antibody program (mRNA-1944) within this modality. However, we do not expect to advance our Chikungunya Antibody program without outside funding, and we are not currently pursuing further development of it at this time.

IL-2 Mutein (mRNA-6231)

IL-2 is a critical cytokine for Treg activation and expansion and our product utilizes subcutaneous mRNA administration to produce a modified version of IL-2 in order to treat autoimmune diseases

IL-2-based therapeutics are being clinically evaluated for a wide range of immune-mediated disorders, including rheumatoid arthritis, systemic lupus erythematosus, graft versus host disease, inflammatory bowel diseases, and autoimmune hepatitis. IL-2 is a cytokine, which are potent modulators of the immune system, directing function and homeostasis. IL-2 is critically important to T cell survival and function. IL-2 acts through a receptor complex that can be dimeric, IL-2Rβ (CD122) plus the common γ chain (CD132), or trimeric, which is formed through the addition of IL-2Rα (CD25) to the dimeric form. The trimeric form has 10-fold to 100-fold greater affinity for IL-2. Under low or homeostatic IL-2 conditions, those cells which preferentially express the trimeric receptor, or IL-2R, such as Tregs and very recently activated effector T cells, are activated.

We believe that our platform can be exploited to produce a modified IL-2 for the treatment of autoimmune conditions. Our modified IL-2 is engineered with mutations that selectively decrease binding to the dimeric IL-2 receptor present on CD4+ and CD8+ T effector cells and NK cells, and increase reliance upon CD25 of the trimeric IL-2 receptor complex to trigger the signaling cascade in regulatory T cells. Our modified IL-2 is also expressed as a fusion protein to extend its half-life in the serum. It is also the first demonstration of subcutaneous administration of the delivery technology that was also used our chikungunya antibody therapeutic, mRNA-1944.

Latest data and next steps

mRNA-6231 is ongoing in a Phase 1 clinical study. The trial is a Phase 1, first-in-human, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of mRNA-6231 in healthy adult participants (between 18-50 years of age), following subcutaneous administration of mRNA-6231.

PD-L1 (mRNA-6981)

PD-L1 is a co-inhibitory receptor that can induce anergy in programmed cell death protein 1 (PD-1)-expressing T cells and we intend to induce expression of PD-L1 on myeloid cells to send a tolerizing signal to immune cells in their environment in order to treat autoimmune diseases

The PD-L1/PD-1 pathway has a critical function in immune regulation and promotes development and function of Tregs. PD-L1 is a transmembrane protein expressed on antigen presenting cells, such as dendritic cells and macrophages, activated T cells, B cells, and monocytes as well as peripheral tissues. Its cognate receptor, PD-1, is a co-inhibitory transmembrane protein expressed on T cells, B cells, natural killer cells and thymocytes. Preclinical mouse models deficient in PD-1 spontaneously develop a variety of autoimmune diseases such as arthritis, myocarditis, lupus-like glomerulonephritis and type 1 diabetes, demonstrating the critical role of the PD-L1/PD-1 interaction in maintaining tolerance to self-antigens. Additionally, treatment of cancer patients with PD-1 or PD-L1 inhibitors sometimes results in immune-related adverse events, including the development of hepatitis, dermatitis and colitis, demonstrating the role of PD-1/PD-L1 in human autoimmune reactions.

We believe our PD-L1 therapy may augment PD-L1 expression on cell types similar to those that endogenously express it, and by reducing immune activation, potentially reduce the clinical manifestations of a variety of autoimmune diseases. Our intent is to use our platform to influence myeloid cells, including dendritic cells, to provide additional co-inhibitory signals by augmenting endogenous expression of PD-L1. We believe that this tolerizing signal to lymphocytes may limit autoreactivity in the context of ongoing autoimmune pathology without severe and global suppression of the immune system. Given that our platform allows us to modify myeloid cells *in situ*, our approach to the creation of a tolerogenic environment may provide unique benefits in treating autoimmune diseases by seeking to restore immune homeostasis.

Latest data and next steps

We have investigated mRNA-6981 in a range of preclinical models of autoimmune and related diseases, including arthritis, type 1 diabetes, colitis and graft-versus-host disease, and observed disease-modifying activity. We are currently in preclinical studies for mRNA-6981.

Relaxin (mRNA-0184)

Relaxin is a vasoactive peptide associated with cardiovascular remodeling and we intend to encode for a relaxin fusion protein to treat decompensated heart failure

Relaxin is a naturally occurring hormone, present in both men and women, that has been shown to promote vasodilation and angiogenesis, regulate extracellular matrix turnover, and suppress arrhythmias post myocardial infarction. Subsequent studies have implicated relaxin's role beyond pregnancy, through vasodilatory, antifibrotic, anti-inflammatory and protective effects on multiple organs. Relaxin activates a variety of pathways, contributing to the reduction of oxidative stress, fibrosis, and inflammation. There is a large body of evidence to support relaxin's clinical potential in several therapeutic areas, with its impact on cardiovascular diseases having been studied in both preclinical and clinical settings. Though prior studies have failed to demonstrate long-term benefit in clinical studies, we believe a novel approach can overcome potential flaws of previous approaches.

mRNA-0184 is being developed to treat decompensated heart failure. Acute heart failure (AHF) is defined as the new onset or worsening of symptoms and signs of heart failure (HF). In developed countries, HF has become a substantial public health problem, affecting 2% of the adult population and AHF is the most frequent cause of unplanned hospital admission in patients of >65 years of age. mRNA-0184 encodes for the relaxin fusion protein. The mRNA sequence of mRNA-0184 is engineered to increase protein expression and prolong half-life.

Latest data and next steps

In preclinical studies, we have shown preliminary protein expression data in nonhuman primates that supports the hypothesis of extended pharmacology relative to historical efforts with recombinant protein. We are planning for a Phase 1 study in participants with chronic heart failure. We expect that mRNA-0814 will be administered after heart failure decompensation to bridge patients through the vulnerable period.

CANCER VACCINES MODALITY

Our cancer vaccines modality currently has three development programs, two of which have entered the clinic. We have regained all rights to our KRAS vaccine (mRNA-5671) from Merck and we are evaluating next steps for the program.

Personalized Cancer Vaccine (PCV) (mRNA-4157)

PCV encodes for up to 34 neoantigens designed against an individual's patient tumor mutations and is ongoing in a Phase 1 and Phase 2 trial across a variety of indications

As tumors grow, they acquire mutations, some of which create new protein sequences, or neoantigens, that can be presented on human leukocyte antigen (HLA) molecules in the tumor and recognized as non-self by T cells. These neoantigens can be shared or are completely unique to an individual patient's tumor. In addition to the neoantigens being unique and patient specific, the presentation of those neoantigens is also dependent on a patient's specific HLA type. Identification of patient-specific HLA type and tumor neoantigens through next generation sequencing paired with our proprietary, *in silico* design of each patient's mRNA vaccine and rapid manufacturing for a specific patient allows us to rapidly deliver a completely unique and personalized medicine to patients.

Our personalized cancer vaccine program, mRNA-4157, consists of an mRNA that encodes up to 34 neoantigens, predicted to elicit both class I (CD8) and class II (CD4) responses, designed against each individual patient's tumor mutations and specific to their HLA type. The neoantigens are encoded in a single mRNA sequence and formulated in our proprietary LNPs designed for intramuscular injection. The mRNA sequence is then manufactured using an automated workflow to enable a rapid turnaround time.

Latest data and next steps

The Phase 1 trial is an open-label, multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in subjects with resected solid tumors and in combination with the checkpoint inhibitor, pembrolizumab (marketed in the United States as KEYTRUDA®), in subjects with resected and unresected solid tumors. mRNA-4157 is administered on the first day of each 21-day cycle for a maximum of nine doses. mRNA-4157 is administered as monotherapy (Part A) or in combination with pembrolizumab (Parts, B, C, and D) in the United States. Studies have shown mRNA-4157 to be well tolerated at all dose levels. The majority of adverse events from mRNA-4157 have been low grade and reversible. Encouraging data emerging from an expansion arm in patients with head and neck cancer has recently caused us to increase the size of that cohort, which continues to recruit trial participants.

The randomized, placebo-controlled Phase 2 study is investigating a 1 mg dose of mRNA-4157 in combination with Merck's pembrolizumab (KEYTRUDA®), compared to pembrolizumab alone, for the adjuvant treatment of high-risk resected melanoma. This study was fully enrolled (N=150) in September 2021 and the primary endpoint of the Phase 2 study is recurrence-free survival at 12 months.

KRAS Vaccine (mRNA-5671)

The Phase 1 study, led by Merck, is ongoing; we have retained all rights to our KRAS vaccine (mRNA-5671) from Merck and we are evaluating next steps for the program.

Oncogenic driver mutations that encode targetable T cell neoantigens have considerable potential therapeutic implications: (1) driver mutations are subject to positive selection, as they confer survival advantages for the tumor, and (2) such neoantigens could be shared between patients, enabling an easier approach to developing and manufacturing such therapeutic or curative interventions.

KRAS is a frequently mutated oncogene in epithelial cancers, primarily lung, colorectal cancer (CRC) and pancreatic cancers. The four most prevalent KRAS mutations associated with these malignancies are G12D, G12V, G13D, and G12C, which constitute 80% to 90% of KRAS mutations.

Latest data and next steps

The Phase 1 open-label, multi-center study to evaluate the safety and tolerability of mRNA-5671 both as a monotherapy and in combination with pembrolizumab, led by Merck, is ongoing. We have retained all rights to our KRAS vaccine (mRNA-5671) from Merck and we are evaluating next steps for the program.

Checkpoint cancer vaccine (mRNA-4359)

We are developing a checkpoint cancer vaccine that encodes antigens for Indoleamine 2,3-dioxygenase (IDO) and programmed death-ligand 1 (PD-L1) antigens

Our checkpoint vaccine aims to stimulate effector T cells that target and kill suppressive immune and tumor cells that express IDO and PD-L1 antigens. Following vaccine-mediated activation, IDO- and PD-L1-specific T cells kill immunosuppressive (regulatory) immune cells and cancer cells. Cancer cell killing and the reduction of regulatory immune cells tip the balance towards productively

inflammatory immune cells with signaling molecules “heating up” the tumor microenvironment, which leads to additional tumor killing by vaccine-activated T cells. T cell priming leads to recognition of additional tumor-associated antigens and to more tumor killing by tumor-specific cytotoxic T cells. Systemic PD-1/PD-L1 blockade may further amplify the effect, leading to further immune activation and superior disease control.

Our initial indications for our checkpoint vaccine are advanced or metastatic cutaneous melanoma and non-small cell lung carcinoma (NSCLC). Melanoma is the fifth most common cancer diagnosis in the U.S. It accounts for approximately 5% of all new cancer diagnoses and 1.5% of all cancer-related deaths. Cutaneous melanoma is a cancer that starts in the melanocytes (pigment-producing cells) of the skin. If diagnosed at the local stage, the 5-year survival rate is approximately 95%. However, for regional or metastatic disease (stage IIIB+), 5-year survival rates decline to approximately 30 to 60%. Approximately 18,000 new patients are diagnosed with stage IIIB+ cutaneous melanoma in the U.S. Advanced melanoma, a rare and serious type of skin cancer, is responsible for most skin cancer-related deaths, despite representing only 1% of skin cancer cases. Current standard of care pembrolizumab, nivolumab or the combination of nivolumab + ipilimumab.

NSCLC frequently goes undetected, remaining asymptomatic until it has progressed to later stages. Approximately 115,000 people are diagnosed with metastatic NSCLC or progress to metastatic disease annually in the United States. The current approach to treatment of metastatic NSCLC treatment is dependent on the presence of PD-L1 expression. If tumor PD-L1 expression is greater than 50% pembrolizumab or atezolizumab monotherapy are preferred, while a combination of chemotherapy and pembrolizumab is preferred for patients with PD-L1 expression less than 50%.

Latest data and next steps

Our checkpoint vaccine is currently in preclinical studies.

INTRATUMORAL IMMUNO-ONCOLOGY MODALITY

Our intratumoral immuno-oncology modality currently has two development programs, both of which are in the clinic.

OX40L/IL-23/IL-36 γ (Triplet) (mRNA-2752)

Triplet includes three mRNAs encoding human OX40L, interleukin 23 (IL-23) and interleukin 36 gamma (IL-36 γ), that are encapsulated in our proprietary LNP and administered intratumorally

Despite recent advances in immune-mediated therapies for cancer, the outlook for many patients with advanced cancer is poor. We are developing Triplet (mRNA-2752) and other programs to drive anti-cancer T cell responses by transforming cold tumor microenvironments into productive, “hotter” immune landscapes with local intratumoral therapies. Triplet (mRNA-2752) utilizes the intrinsic advantage of mRNA to multiplex and to produce membrane and secreted proteins with mRNA in a single investigational medicine. Triplet (mRNA-2752) includes three mRNAs encoding human OX40L, IL-23 and IL-36 γ that are encapsulated in our proprietary LNP and administered intratumorally. OX40L is a membrane protein, whereas IL-23 and IL-36 γ are secreted cytokines. We believe our approach has the advantage of localized high concentration gradients of IL-23 and IL-36 γ compared to recombinant proteins administered systemically or intratumorally. Additionally, the mRNA for OX40L encodes for the wild type membrane protein, which we believe recombinant protein technologies cannot enable.

We are developing Triplet (mRNA-2752) for the treatment of advanced or metastatic solid tumor malignancies or lymphoma as a single agent or in combination with checkpoint inhibitors.

Latest data and next steps

mRNA-2752 is ongoing in a Phase 1 open-label, multicenter, dose-escalation study. This study is evaluating the safety and tolerability of escalating intratumoral injections of mRNA-2752 alone and in combination with PD-L1 inhibitor (durvalumab) to define the maximum tolerated dose (MTD) or a recommended dose for expansion (RDE). The study consists of dose escalation and dose confirmation parts, which will occur in Arm A and Arm B, followed by a dose expansion part, which will occur in Arm B, and a Dose Exploration in Arm C as a neoadjuvant therapy for cutaneous melanoma. Enrollment in the dose expansion part of Arm B and Arm C is currently ongoing.

We previously announced the interim results of Part A in 2020. In 2021, we announced that the Phase 1 study demonstrates that Triplet given in combination with AstraZeneca’s durvalumab (IMFINZI®) was tolerated at all dose levels tested and elicited evidence of anti-tumor activity. The recommended dose for expansion (RDE) is up to 4mg mRNA-2752 + durvalumab. The study also demonstrated evidence of immunomodulation and expected pharmacodynamics in the tumor immune microenvironment (TME) of both injected and un-injected lesions, in both monotherapy and combination cases, as indicated by increases in proliferating (activated)

T cells, PD-L1 levels (marker of interferon signaling), and T cell-inflamed (GEP) and DC transcriptional signature score, with greatest changes observed in patients with clinical benefit.

IL-12 (MEDI1191)

In collaboration with AstraZeneca, we are developing a mRNA that encodes for IL-12 encapsulated in our proprietary LNP delivered intratumorally

Another strategy for cancer patients with immunologically cold tumors is to transform the tumor microenvironment by introducing pro-inflammatory cytokines directly into tumors or draining lymph nodes. In collaboration with AstraZeneca, we are developing MEDI1191, which is an mRNA for IL-12 encapsulated in our proprietary LNP to be delivered intratumorally. Systemic administration of recombinant IL-12 protein was poorly tolerated in early clinical trials and exhibited generally low response rates. MEDI1191 can enhance the immune response by positively impacting both antigen presenting cells and T cells, and local, intratumoral expression of IL-12 can potentially improve tolerability compared to systemic protein treatments.

MEDI1191 is being developed for the treatment of advanced or metastatic solid tumors in combination with a checkpoint inhibitor. MEDI1191 consists of our proprietary LNP encapsulating an mRNA for human IL-12B (p40) and IL-12A (p35) subunits. The mRNA produces a single-chain fusion protein of the IL-12B and IL-12A subunits, with a linker between the subunits. The mRNA sequence has been engineered to enhance protein production and is designed to decrease the amount of protein that might be made in hepatocytes for better tolerability.

Latest data and next steps

In preclinical studies, treatment with IL-12 transformed the tumor microenvironment, with notable activation of natural killer and dendritic cells, and an increase in cytotoxic lymphocytes. AstraZeneca is leading the early clinical development and an open-label multicenter Phase 1 clinical trial of intratumoral injections of MEDI1191 alone and in combination with the checkpoint inhibitor, durvalumab, is ongoing. In 2021, we presented IL-12 data that show evidence of antitumor activity in injected and non-injected lesions as well as pharmacodynamic effects such as increased IL-12, Interferon gamma (IFN γ) and 12, and inflammatory transcriptome.

REGENERATIVE THERAPEUTICS MODALITY

Our regenerative therapeutics modality currently has one development program, which is in the clinic.

VEGF-A (AZD8601)

In collaboration with AstraZeneca, VEGF-A is a localized therapeutic encoding for the VEGF-A protein and addressing ischemic heart failure

Heart disease is the leading cause of death in the United States, accounting for one in every four deaths, and is often due to the inability of adults to regenerate heart tissue. Current approved therapies do not specifically address heart regeneration. Previous attempts at cardiac regeneration have included stem cell grafting and gene therapy, but have faced challenges with safety or efficacy. Several treatments are available for patients with ischemic heart failure. Current treatments include revascularization of the coronary arteries to relieve symptoms and improve cardiac function and therapies that reduce blood pressure or potentially help eliminate excess fluids in congested tissues, including: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, and aldosterone receptor blockers as diuretics. However, adult humans are unable to regenerate myocardium tissue following injury and the treatment options described above cannot compensate for this.

Vascular Endothelial Growth Factor A (VEGF-A) is a potent angiogenic factor that promotes growth of blood vessels and acts as a powerful promoter of blood vessel growth. Systemic injection of VEGF-A protein increases VEGF-A exposure throughout the body, which can lead to side effects, but is very short-lived in circulation. Therefore, any therapy involving VEGF-A needs to be localized to elevate local protein concentration and drive revascularization while minimizing systemic side effects. AstraZeneca has opted to pursue the localized application of VEGF-A mRNA in a simple saline formulation in the heart muscle to elevate local protein concentration for longer periods due to increased local protein production. This potentially allows for an extended pharmacodynamic effect at the specific site of injection compared to systemic or local administration of a recombinant protein version of VEGF-A.

Latest data and next steps

Preclinical studies have been conducted at AstraZeneca in models of ischemic heart failure. In mouse, rat, and pig models of myocardial infarction, direct injection in the heart muscle (myocardium) of VEGF-A mRNA led to elevated cardiac VEGF-A protein levels and improved cardiac function. The Phase 1a/b study was a randomized, double-blind, placebo-controlled study in men with type 2 diabetes mellitus conducted in Europe. VEGF-A mRNA was administered by intradermal injection into the forearm skin in single ascending doses. Administration of AZD8601 demonstrated protein production and changes in local blood flow in diabetic patients. Tolerability of our mRNA injected intradermally was demonstrated for all dose levels. The only causally treatment-related adverse events were mild injection-site reactions, occurring in 32 of 33 participants receiving VEGF-A mRNA across both parts of the study design. All adverse events of injection-site reaction were of mild intensity. No deaths, serious adverse events, or adverse events leading to discontinuation occurred.

AstraZeneca has also progressed VEGF-A (AZD8601) to a randomized, placebo-controlled, double-blind, multicenter, 6-month, Phase 2a clinical trial of the safety, tolerability, and exploratory efficacy of epicardial injections of AZD8601 in patients with stable coronary artery disease and moderately decreased left ventricular ejection fraction (LVEF) who are undergoing coronary artery bypass graft surgery. Exploratory efficacy endpoints included LVEF, NT-proBNP (a biomarker which measures the level of a hormone which is elevated in patients with heart failure), and functional patient reported outcomes. In 2021, the Phase 2 study met the primary endpoint of safety and tolerability of AZD8601 for the 3 mg dose. In the study of 11 patients, seven were treated with AZD8601 VEGF-A mRNA and four received placebo injections. Numerical trends were observed in endpoints in the heart failure efficacy domains compared with placebo, including increase in LVEF and patient reported outcomes. In addition, all seven patients treated with AZD8601 had NT-proBNP levels below heart failure (HF) limit at 6 months follow-up compared to one of four patients treated with placebo. AstraZeneca has announced that they intend to move AZD8601 into further studies.

SYSTEMIC INTRACELLULAR THERAPEUTICS

Our systemic intracellular therapeutics modality currently has five development programs, two of which are in the clinic.

Propionic acidemia (PA) (mRNA-3927)

PA is an inherited metabolism disorder with significant morbidity and mortality and our mRNA therapy is ongoing in a Phase I trial, aiming to produce an intracellular, mitochondrial enzyme complex to treat the disorder

PA is a serious inborn error of metabolism disorder with significant morbidity and mortality. There are approximately 325-2,000 PA patients in the United States based on estimated birth prevalence (0.2-1.2:100,000 newborns) and mortality rates. The vast majority of patients present with life-threatening metabolic crises during the first few days or weeks of life, with mortality rates ranging from 13-53% during the neonatal period. The cardinal feature of the disorder is the occurrence of life-threatening acute metabolic decompensations that are more frequent in the first few years of life. Longer term sequelae include cardiac complications (cardiomyopathy, arrhythmias) and severe neurologic complications. The disorder is caused by a defect or deficiency in PCC, an enzyme that is one step upstream in the same metabolic pathway as the MUT enzyme that is deficient in MMA, as further described below. PCC is a complex hetero-dodecamer enzyme composed of six alpha subunits (PCCA) and six beta subunits (PCCB). The disorder is autosomal recessive, with PA patients generally having loss-of-function mutations in either PCCA or PCCB (and in rare instances, mutations in both PCCA and PCCB). The disorder is biochemically characterized by the accumulation of toxic metabolites such as 3-hydroxypropionic acid and 2-methylcitrate, among others, and these metabolites may be used as biomarkers of disease. There is no approved therapy for PA to treat the underlying defect, including no enzyme replacement therapy, due to the complexity of PCC and mitochondrial localization.

We are developing an IV-administered combination mRNA approach, which contains two mRNAs, one for each of the subunits of PCC (PCCA and PCCB) encapsulated in our proprietary LNP (the same LNP formulation as mRNA-1944). The intent is to potentially treat the entire PA population, regardless of whether an individual has a defect or deficiency in the PCC alpha or beta subunit. The mRNA sequences have been engineered to improve protein translation and encode enzymatically-active PCC with the proper subcellular localization in the mitochondria.

Latest data and next steps

We have demonstrated activity in a PA mouse model in a long-term repeat dose study. In the 6-month repeat dose study in PA mice, a significant and sustained lowering of additional disease biomarkers (e.g., 2-methylcitrate, or 2MC) was observed throughout the duration of the 6-month study. mRNA-3927 is ongoing in a Phase 1/2 study, the Paramount Study, and the first cohort is fully enrolled, and cohort 2 enrollment is ongoing. The study's objective is to evaluate the safety and pharmacology of mRNA-3927 in patients 1 year of age and older with PA. The primary endpoints are safety and pharmacokinetics and pharmacodynamics. Secondary endpoints include incidence and severity of adverse events (AEs) and change in plasma biomarkers: methylcitric acid (2-MC) and 3-Hydroxypropionic acid (3-HP). We have received Rare Pediatric Disease Designation, Orphan Drug Designation and Fast Track Designation from the FDA and Orphan Drug Designation from the European Commission for the PA program.

Methylmalonic acidemia (MMA) (mRNA-3705)

MMA is an inherited metabolism disorder with significant morbidity and mortality and our mRNA therapy is ongoing in a Phase 1 trial, aiming to produce an intracellular, mitochondrial enzyme complex to treat the disorder

There are an estimated 500-2,000 MMA MUT deficiency patients in the United States based on estimated birth prevalence (0.3-1.2:100,000 newborns) and mortality rates. Mortality is significant, with mortality rates of 50% for MMA patients with complete MUT deficiency (mut⁰) (median age of death 2 years) and 40% for MMA patients with partial MUT deficiency (mut⁻) (median age of death 4.5 years) reported in a large European study. MMA mainly affects the pediatric population and usually presents in the first few days or weeks of life. The occurrence of acute metabolic decompensations is the hallmark of the disorder and decompensations are typically more frequent in the first few years of life. Each decompensation is life-threatening and often requires hospitalization and management at an intensive care unit. Surviving patients often suffer from numerous complications including chronic renal failure and neurologic complications such as movement disorders, developmental delays, and seizures. Consequently, the health-related quality of life for MMA patients and their families is significantly impaired.

The disorder is autosomal recessive and primarily caused by loss-of-function mutations in the gene encoding MUT, a mitochondrial enzyme that metabolizes certain proteins and fats, resulting in complete (mut⁰) or partial (mut⁻) enzyme deficiency. There are currently no approved therapies that address the underlying defect for MMA.

We are developing an mRNA encoding human MUT encapsulated in our proprietary LNPs for IV administration for the treatment of isolated MMA associated with MUT deficiency. The sequence has been engineered to improve protein translation. To function, the mRNA-encoded MUT protein is translocated to its site of action in the mitochondria. mRNA-3705 is our second generation MMA development candidate.

Latest data and next steps

We previously demonstrated, in a series of *in vitro* and *in vivo* pharmacology studies, that human MUT mRNA effectively directs the biosynthesis of active MUT protein with physiologically correct mitochondrial localization *in vitro*, and improves survival and corrects biochemical abnormalities in two different mouse models of MMA representing the spectrum of MUT deficiency (mut⁰ and mut⁻). Technology and process improvements enabled the development of an updated drug product, mRNA-3705, which shows greater potency and better pharmacology compared to our prior candidate, mRNA-3704. mRNA-3705 is currently ongoing in a Phase 1/2 study, the Landmark Study. The study is an adaptive, open-label study designed to evaluate the safety and tolerability of up to five different dosing regimens of mRNA-3705 administered via intravenous infusion in patients one year and older with isolated methylmalonic acidemia due to methylmalonyl-CoA mutase (hMUT). Upon establishment of an optimized dose based on safety and pharmacological data, additional patients may be enrolled in an optional expansion cohort.

Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

GSD1a is an inherited metabolism disease and our approach is to use an mRNA encoding for intracellular human glucose 6-phosphatase

GSD1a is an inherited metabolic disorder caused by a deficiency in the catalytic activity of G6Pase. G6Pase catalyzes the hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate, the final step of glycogenolysis and gluconeogenesis that mainly takes place in the liver and kidneys. GSD1a patients suffer from severe fasting hypoglycemia, hepatomegaly, nephromegaly, lactic acidemia, hypertriglyceridemia, hyperuricemia, hypercholesterolemia, hepatic steatosis, and growth retardation. In addition, hepatocellular adenomas occur in 70% to 80% of GSD1a patients by their third decade of life and carries risk of transformation into hepatocellular carcinomas. Proteinuria has been observed in over half of patients above 25 years of age. GSD1a occurs in approximately 1:100,000 live births in the United States and European Union but is more common in Ashkenazi Jews where the incidence is reported to be 1:20,000 live births. There are an estimated 2,500 people in the United States and over 4,000 people in the European Union with GSD1a. Although strict diet therapy, including frequent feeding with uncooked cornstarch, allows GSD1a patients to live into adulthood by preventing hypoglycemia, the underlying pathological processes remain uncorrected resulting in the development of many long-term complications including liver adenomas and hepatocellular carcinoma.

Our program, mRNA-3745, consists of an mRNA encoding for modified human G6Pase encapsulated in our proprietary LNPs. The human G6Pase sequence is modified for improved protein production and G6Pase activity. mRNA-3745 is designed to be administered intravenously and encodes G6Pase protein to restore this deficient or defective enzyme.

Latest data and next steps

We have conducted several *in vitro* and *in vivo* pharmacology studies to demonstrate preclinical proof-of-concept for GSD1a therapy. mRNA encoding for G6Pase introduced in human cells resulted in robust production of active G6Pase with subcellular localization into endoplasmic reticulum. mRNA-3745 has been granted Orphan Drug Designation by the U.S. FDA as well as the European Medicines Agency (EMA) and has an open IND. The Phase 1 study will evaluate the safety and pharmacology of mRNA-3745 in patients 18 years of age and older with GSD1a. The Phase 1 study, the Balance Study, is a single dose escalation study in adult participants diagnosed with GSD1a. The primary objective is to determine the safety and tolerability following a single dose of mRNA-3745. Secondary objectives are to evaluate pharmacokinetics and pharmacodynamics of mRNA-3745 in adult GSD1a patients.

Phenylketonuria (PKU) (mRNA-3283)

PKU is a rare inherited metabolic disease is and our approach is to use an mRNA encoding for intracellular phenylalanine hydroxylase (PAH)

Phenylketonuria (PKU) is a rare inherited metabolic disease resulting from a deficiency in the metabolism of phenylalanine (PHE) due to mutations within the enzyme phenylalanine hydroxylase (PAH). The most effective treatment is a restrictive diet of low protein, which controls PHE intake. Approximately 20-56% of PKU patients respond to sapropterin dihydrochloride (marketed as Kuvan in the United States), a synthetic BH4 cofactor for PAH which improves PHE metabolism, but does not fully cure patients. In addition, in May 2018, Biomarin received approval for pegylated phenylalanine lyase (PAL), marketed as Palynziq. Palynziq is a pegylated recombinant bacterial enzyme which metabolizes PHE in the blood. We believe the immune risk is, at least in part, driven by bacterial PAL. PKU occurs in approximately 1:10,000-15,000 live births in the United States. Based on current population estimates that would translate into approximately 21,000-32,000 PKU patients in the United States. Affected individuals have a deficiency in the enzyme PAH, resulting in a reduced or complete inability to metabolize the essential amino acid phenylalanine into tyrosine. Thus, PKU patients suffer from a phenylalanine intoxication and a subsequent deprivation of tyrosine, leading to severe mental disability if left untreated.

Our program mRNA-3283 consists of an mRNA encoding human PAH encapsulated in our proprietary LNPs. The mRNA sequence is optimized for protein synthesis and contains a microRNA binding site to reduce or potentially eliminate synthesis of protein outside of the target tissues. mRNA-3283 is designed to be administered intravenously to encode enzymatically-active PAH protein in liver to restore this deficient or defective enzyme.

Latest data and next steps

We have conducted several *in vitro* and *in vivo* pharmacology studies to demonstrate preclinical proof-of-concept for PAH therapy. A PKU mouse model demonstrated a significant reduction of blood PHE levels post dose. mRNA-3283 is ongoing in preclinical studies.

Crigler-Najjar Syndrome Type 1 (CN-1) (mRNA-3351)

CN-1 is a severe condition caused by the mutations in the UGT1A1 gene and our approach, in collaboration with the Institute of Life Changing Medicines (ILCM), is to encode for the human UGT1A1 protein

Crigler-Najjar syndrome is a severe condition characterized by high levels of a toxic substance called bilirubin in the blood (hyperbilirubinemia). It is caused by the mutations in the UGT1A1 gene in which bilirubin, a substance made by the liver, cannot be broken down. Without this enzyme, bilirubin can build up in the body and lead to jaundice and damage to the brain, muscles and nerves. The symptoms become apparent shortly after birth and can be life-threatening. It is estimated that there are only approximately 70-100 known cases of CN-1 in the world. Affected individuals rely on current standard of care, phototherapy treatments of up to 12 hours a day, throughout life. The only definitive treatment is liver transplant that is associated with its own set of side effects and risk of death.

Our program, mRNA-3351, consists of an mRNA encoding human UGT1A1 encapsulated in our proprietary LNPs. It is designed to restore the missing or dysfunctional proteins that causes CN-1.

Latest data and next steps

We have licensed mRNA-3351 to ILCM with no upfront fees and without any downstream payments. The goal of the collaboration is to make an mRNA therapy for the treatment of CN-1 available at no cost to patients. ILCM will be responsible for the clinical development of mRNA-3351.

INHALED PULMONARY THERAPEUTICS

Our inhaled pulmonary therapeutics modality currently has one development candidate.

Cystic Fibrosis (CF) (VXc-522)

CF is a multi-system disease caused by the mutations in the CFTR gene and our approach, in collaboration with Vertex, is to deliver mRNA to the lungs to provide functional CFTR protein expression that translates to transformative clinical benefit

CF is a rare genetic disease, which is progressive from birth and leads to multi-organ damage and early death due to lung dysfunction. It is caused by the mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which results in the loss of CFTR chloride ion channel function. This decreased function of CFTR at the cell surface leads to thick, sticky mucus in multiple organ systems but most pathologically the lungs. It is estimated that there are ~75,000 patients with cystic fibrosis in the world, with ~10% of these patients not addressable with the approved CFTR modulators.

Our program is designed to treat the underlying cause of CF by enabling cells in the lungs to produce functional CFTR protein for the treatment of the 10% of patients who do not produce any modulator-responsive CFTR protein.

Latest data and next steps

We are collaborating with Vertex on our CF candidate, VXc-522. Pre-clinical studies are ongoing and Vertex expects to submit an IND in 2022.

MANUFACTURING

Manufacturing plays a critical role in our value chain and our ability to develop a new class of medicines. Our manufacturing capabilities support every stage of the development of our products, from new product ideas to commercialization. During the research stage of product development, manufacturing provides mRNA drug substance and drug product for platform research and therapeutic area drug discovery. During early development of our investigational medicines, we manufacture mRNA and drug product for IND-enabling GLP toxicology studies and initial human clinical studies. For late clinical development, we produce mRNA and drug product for phase 3 studies. At the commercial stage of development, we manufacture drug substance and drug product in collaboration with our contract manufacturing organizations (CMOs), both in the U.S. and internationally.

Our approach to date has been to proactively invest and build manufacturing capacity internally and externally with our network of strategic partners in anticipation of demand. This capacity was immediately leveraged and expanded during our COVID-19 vaccine ramp-up into a commercial product in response to the ongoing pandemic. Our ability to rapidly accelerate our manufacturing capabilities in response to COVID-19 allowed us to ship 807 million doses of our COVID-19 vaccine globally in 2021, compared to 17 million doses in December 2020. We are committed to further increase our manufacturing capacity substantially in 2022.

Overview of our manufacturing operating model

Our manufacturing activities generally focus on the following:

- **Commercial Production:** Our manufacturing expertise includes state-of-the-art technologies for mRNA and drug product manufacturing, as well as quality control testing to attain a robust and consistent supply that matches target product profiles. Our manufacturing technology is built to scale-up and support industrialization of products for commercial approval.
- **Research and Development Support:** The product supply enables platform research and drug discovery in our therapeutic and vaccine areas, in addition to activities related to clinical studies of our investigational medicines.

Given our expectations for significant ongoing pipeline expansion and the long lead time required to build manufacturing infrastructure, we built a dedicated in-house manufacturing facility in Norwood, MA, the Moderna Technology Center (MTC), which we have since expanded to a multi-building campus. The MTC provides supply for our preclinical research, IND-enabling GLP toxicology study supplies, our Phase 1 and Phase 2 pipeline activities, later-stage clinical development activities (e.g., Phase 3 CMV vaccine clinical trials), as well as COVID-19 vaccine drug substance production.

The MTC campus has been designed with a high level of automation and state-of-the-art digital integration to handle manufacturing execution, product testing and release, and regulatory filings. In addition, substantial manufacturing capabilities are realized via CMO relationships in the United States and abroad, providing drug substance and fill-finish capacity for the COVID-19 vaccine. Much of the production for our COVID-19 vaccine supply for the U.S. market is completed at the MTC campus, with additional production by Lonza Ltd. (Lonza). We have also partnered with Lonza to complete production in Switzerland of our COVID-19 vaccine for markets outside the United States, as well as with National Resilience, Inc. to manufacture drug substance at its facility in Ontario, Canada for distribution worldwide. Fill-finish services for our COVID-19 vaccine are provided by Catalent Inc., Thermo Fisher Scientific, Sanofi and Baxter BioPharma Solutions in the United States, and by ROVI (in Spain), Recipharm (in France) and Samsung Biologics (in South Korea) outside the United States. We have also partnered with other CMOs for the production of and fill-finish services of our COVID-19 vaccine, and expect that we will enter into additional collaborations as we continue to scale. In April 2021, we announced additional investments in manufacturing to increase supply at our owned and partnered manufacturing facilities, with the goal of increasing our global 2022 capacity for COVID-19 vaccine production. In May 2021, we announced the planned expansion of the MTC, which we expect to more than double the space at the MTC and allow us to continue to optimize our mRNA products as we explore new pharmaceutical delivery forms such as prefilled syringes and lyophilized products. Additionally, in February 2022, we announced new collaborations with ROVI and Thermo Fisher Scientific (Thermo Fisher) for manufacturing capabilities. With ROVI, we agreed to a ten-year collaboration to increase manufacturing capacity at ROVI's facilities in Spain. In addition to producing our COVID-19 vaccine, we expect that ROVI's platform may be utilized to service other vaccine candidates in the future. With Thermo Fisher, we agreed to a fifteen-year collaboration to enable dedicated large-scale manufacturing in the United States of our COVID-19 vaccine and other investigational mRNA medicines in our pipeline.

In addition, during 2021 we announced agreements in principle with the governments of Canada and Australia to establish mRNA manufacturing facilities in those countries. These agreements are subject to final negotiation, but we envision entering into long-term supply agreements with these countries for the supply of mRNA vaccines. By establishing manufacturing facilities locally, we will also provide these governments with direct access to rapid pandemic response capabilities. We are in active discussions with other governments to provide similar manufacturing capabilities in other geographies.

We have further committed to building a state-of-the-art mRNA facility in Africa to provide a local source of mRNA medicines for the continent, in part to prepare for future pandemics. We expect to invest up to \$500 million in this facility and anticipate that once fully operational, it will be capable of producing up to 500 million doses of vaccines annually at the 50 µg dose level.

Manufacturing technology development

To support our broad pipeline of products, which span multiple therapeutic areas and routes of administration (e.g., intramuscular, intratumoral, and intravenous), there is close collaboration between our platform research and technical development teams to facilitate rapid and seamless clinical translation of scientific breakthroughs. This, in turn, enables us to develop potential vaccines and therapies to serve a widening patient population.

Technical development encompasses the design and optimization of robust and consistent manufacturing processes, product characterization, fit-for-purpose formulations, and product presentations. For instance, our novel hardware platforms' automation and robotics, coupled with the flexibility of our in-house digital development systems, allows for thousands of experiments and process parameters across our projects, thus supporting our drug product pharmaceutical readiness. Moreover, our recent technical manufacturing advances have enabled internalization of new key capabilities, including DNA plasmids and small molecules.

In parallel, we have refined existing processes, resulting in increased manufacturing scale and more robust stability of our mRNA and drug product. These improvements allow us significant control over our supply chain, resulting in larger production yields and longer shelf life of our products. Furthermore, formulation development advancements have added new drug product images, including lyophilization, giving us a path from frozen to refrigerated storage conditions.

Our substantial investments in recent years in technical development has enabled the breadth and depth of our pipeline, and laid the foundation to help meet the needs and requirements associated with late stage development and the commercialization of the COVID-19 vaccine.

Supply of mRNA for All Stages of Product Development and Commercialization

Supply for Research

High-throughput automation and custom engineered equipment allow us to produce and deliver high quality mRNA and formulated constructs in a short period of time: our proprietary platform is capable of producing up to 1,000 lots of mRNA sequences and formulations per month with a turnaround time of a few weeks from sequence to final product. The typical scale of mRNA manufactured by this team is 1–1,000 mg. This has been possible, in part, thanks to the ability of researchers in the Moderna ecosystem to order constructs through an integrated digital portal that tracks materials end-to-end in less than 45 days. In addition, multiple integrated algorithms that leverage artificial intelligence and machine learning optimize manufacturability, reduce failures, and increase quality of mRNA sequences.

Supply for Early Development

We have established manufacturing capabilities that support the early development stage of product development in three key areas: GLP Tox, Clinical Studies, and Personalized Cancer Vaccines. We supply mRNA and formulated product to conduct IND-enabling GLP toxicology studies. In addition, human clinical studies rely on supply to meet required cGMP standards. This is achieved via internal manufacturing at the MTC and external manufacturing at well-established CMOs. We select specialized CMOs to support our portfolio. We will continue to selectively partner with CMOs to complement our capacity and provide supply contingency where needed. Our MTC facility is also suited to enable rapid technology development and scale-up for future needs. Our manufacturing also produces cGMP PCVs. Due to the specialized nature of personalized medicine (i.e., where a batch is specifically designed and manufactured for a single patient), the manufacturing Personalized Vaccine Unit (PVU) has unique requirements. We digitally integrate patient-specific data from sequencing tumor samples to automatically design PCVs for patients. We have developed proprietary bioinformatics designed algorithms linked to an automated manufacturing process for rapid production of formulated mRNA, with a typical turnaround time of a few weeks. We have operationalized PCV manufacturing at the MTC campus to meet our Phase 1 and 2 pipeline supply needs by using single-use systems with fast “needle-to-needle” turnaround times. Unlike traditional process development, each PCV batch is manufactured for a single patient and thus scaled-out (in parallel) with extensive use of automation and robotics to account for the larger number of patients involved in later phases of development and commercialization. We have shown consistent quality in our production of over 160 patient batches, each with unique mRNA sequences.

These capabilities have allowed us to build our broad pipeline of 44 development programs, including the output required to supply related toxicological and human clinical studies. While the technology that underpins these programs is the same, each program typically requires customization based on target product profiles. These custom features range from varying molecular architecture to different routes of administration, often requiring multivalent products. For example, our CMV vaccine (mRNA-1647) requires six different mRNA sequences to be manufactured for inclusion in an intramuscular mRNA medicine, whereas our COVID-19 vaccine (mRNA-1273) requires a single mRNA sequence for inclusion in an intramuscular mRNA medicine. All programs, with the exception of PCV, require that we progressively scale up supply to meet clinical demand requirements across development phases, in addition to

the necessary preparation for regulatory approval and commercial production, which demand larger batch sizes. In contrast, the PCV program seeks to develop a cancer vaccine that is designed and manufactured for a specific patient, thus increasing the number of unique batches. As we scale manufacturing output for each program, we plan to continuously improve yield, purity, and the pharmaceutical properties of our development candidates.

Supply for Late-Stage Development and Commercialization

As we continue to manufacture our COVID-19 vaccine, our development pipeline continues to advance to later-stage development and towards commercialization. Our platform approach allows us to continue to evolve our manufacturing suites and other capabilities at our MTC campus. Building expansions and enhancements have continued throughout scale-up of our COVID-19 vaccine manufacturing capabilities. The modular nature of the MTC suites permits us to manufacture multiple products in parallel. For instance, we can produce drug substance and drug product for our phase 3 CMV clinical trial while manufacturing COVID-19 drug substance in the same facilities.

Quality Unit

Quality is core to the way we operate. We seek to ensure quality at Moderna through a combination of a robust Quality Management System (QMS), our quality culture, and our people. In accordance with applicable regulations, we have established, documented, and implemented a QMS to assure continued compliance with the requirements therein. The QMS facilitates cGMP compliance by implementing practices that identify the various required processes, their application throughout the organization, and the sequence of interaction of these processes.

The primary mode of documenting these key practices is through policies, standard operating procedures (SOPs), forms, and other quality records, which include an overarching Quality Policy and Quality Manual. We have implemented measurement tools and metrics to monitor, measure, and analyze these practices to support cGMP operations, achieve planned results, and support continuous improvement. We monitor these quality metrics through formal governance processes, including Quality Management Review (QMR), to enable continuous improvement. We have also established an independent Quality Unit that fulfills quality assurance and quality control responsibilities.

Our Quality Unit grew into an international organization with the introduction of COVID-19 vaccine manufacturing. Quality drives our quality culture and ensures it is applied consistently and thoughtfully across the globe.

While the Quality Unit is ultimately accountable and responsible for quality, this is a shared responsibility. All cGMP personnel are empowered to ensure quality systems are appropriately maintained and executed.

We have established a culture that encourages transparency, accountability, and ownership of quality at all levels in the organization. As we scale the quality organization, we have focused on hiring the best talent with the required experience, training, and education.

Supply Chain Unit

We have established an international supply chain to enable supply of the raw materials used to produce our mRNAs and the components of our formulations, securing supply for COVID-19 vaccine alongside clinical and preclinical demands. We have worked with our supply chain vendors to characterize critical raw materials and to understand their impact on the quality of mRNA drug substance and formulated drug product. We also assess the quality system and performance of our supply chain vendors and work with them to comply with regulatory requirements.

DIGITAL INFRASTRUCTURE

We believe that digital technologies, such as robotics, automation, artificial intelligence (AI) and cloud computing, are critical to operationalize our strategy, accelerate our pace of learning and execute at scale. We aspire to digitize our operations wherever possible, with the goal of using the power of digital technology to maximize our impact on patients. Since our inception, we have invested heavily in our digital technologies, robotics/automation, analytics, data science and AI. To facilitate our growth, we will continue to invest in our digital infrastructure. Construction has begun on our new Moderna Science Center in Cambridge, which is designed to integrate digital-first scientific research and development labs. Our approach to bring these digital technologies into our workflows and processes has involved the following:

- utilization of a consistent set of digital building blocks;
- application of digital technologies in multiple business processes; and
- rapid iterations for maximum optimization.

We have seen several benefits from our investments in digitization, most importantly through the depth of our platform technology and breadth of our pipeline. Other benefits include:

- **Quality:** Reduction in human errors by enabling automation, repeatability, and seamless integration;
- **Scalability:** Growth in our pipeline to 44 development programs;
- **Speed:** Rapid manufacture of cGMP product, as exhibited by our first COVID-19 vaccine batch, and research-grade mRNA; and
- **Cost efficiencies:** Digital infrastructure utilized across our platform, drug discovery, clinical development, and manufacturing to maximize efficiencies.

Our digital building blocks

We utilize six building blocks for our digital infrastructure:

- *Cloud enablement* is a critical component of our digital infrastructure. We are at the forefront of mRNA technology. We generate complex data sets, and our scientists need computational power and agility to operate without being limited by traditional computing technology. Maintaining digital infrastructure in the cloud provides the benefits of lower costs by simplifying provisioning and administration, flexibility, scalability, ease of maintenance, disaster recovery, and information security.
- *Integration of business processes* enables us to streamline processes and bring data together in a consistent manner, avoiding caches of information and manual intervention. This efficient flow of data between systems enables the automation of our business processes.
- *Internet of things* allows for smart interconnected devices that provide real-time synchronization of operations. The data from equipment provides real-time guidance to our scientists and engineers and helps us in supply chain and manufacturing with compliance and traceability, including tracking material, controlling inventory and optimizing instrument usage.
- *Automation* allows us to scale our operations reliably and reproducibly. With the help of custom hardware solutions and state-of-the-art robotics, we can continue to increase our operating efficiency, reduce errors, and improve our quality and compliance.
- *Advanced analytics* enable us to draw insights from our data. We are constantly generating large data sets that can provide important insights if mined appropriately and regularly.
- *AI* is enabling key breakthroughs in predictive modeling. It will allow us to improve our mRNA design algorithms based on machine learning, and will provide us with critical insights into research, supply chain, manufacturing, and other processes.

Digital technologies to enable our drug discovery efforts

We have deployed multiple digital technologies to drive a rapid pace of learning, enable efficient workflows and business processes, and draw insights from vast amounts of data. Our aim is to provide our platform and discovery scientists with access to an environment that helps them through each step of their research cycle.

Drug Design Studio: Our proprietary in-house digital application suite contains a Sequence Designer module to tailor an entire mRNA, with ever-improving rule sets that contain our accumulated learning about mRNA design. Drug Design Studio utilizes cloud-based computational capacity to run various algorithms we have developed to design each mRNA sequence. The utility of cloud-based capacity allows us to provide flexible computational capacity on demand, allowing us to power parallel intake and design of multiple mRNA sequences. Once a sequence is designed, it can be ordered digitally using an internal order form application within Drug Design Studio.

Manufacture of research-grade mRNA: Once an order is optimized, the mRNA production process is triggered. We have developed proprietary interfaces that allow the manufacturing team to track production orders at every stage. We have automated several manufacturing steps using both off-the-shelf and custom automation. The equipment used in the manufacture of research-grade

mRNA is integrated with the digital interfaces to capture, extract, and interpret the data generated at each step of the manufacturing process, building digital traceability on each mRNA order. We have also embedded real-time algorithms and analytics tools to allow for automated decision-making at some stages, accelerate the quality control workflows, and provide for continuous improvement of manufacturing processes.

Dispatching and shipping mRNA: Because we produce large quantities of research-grade mRNA, we require digital tools to track their shipment to our scientists and to external contract research organizations (CROs) conducting *in vivo* studies. Our dispatching and shipping application automatically generates bar-coded labels, allowing for traceability of product.

Inventory and registry: Material used in research and created in production, including mRNA, cell lines, chemicals, and reagents, is tracked in our Inventory application. This application supports numerous workflow tools such as consumption, aliquoting, material transfer, and stock alerts. Critical material types are assigned unique registry identification by our Registry application.

Study design: Using our Drug Design Studio, our scientists can design their *in vivo* studies using our proprietary Study Design application. This application captures *in vivo* study protocol design parameters, including dose amount, number of doses, frequency, samples, and assays for each sample. This application serves two purposes. It allows our scientists to maintain and track their *in vivo* study designs and associated research grade mRNA. Our Study Design application also allows our *in vivo* pharmacology teams to track the various ongoing studies and leverage external CROs to manage the *in vivo* demand as needed.

Experiment management: We have deployed Electronic Lab Notebooks for experiment management, allowing our scientists to streamline documentation of their experiments and track it in a standardized, searchable repository. We have also integrated Electronic Lab Notebooks further with our other research tools to connect inventory, *in vivo* studies, and instrument data.

Advanced analytics and AI to accelerate the pace of learning: We utilize AI to enable various parts of our platform and drug discovery. Examples include:

- **Neural networks for protein engineering:** One way to optimize the efficacy of the proteins encoded by our mRNA is to engineer the sequence of the protein itself. We use neural networks to analyze and model protein sequences. We train these models by inputting orthologous sequences from thousands of organisms, from which we can generate potential protein sequences optimized for specific attributes.
- **Neural networks for mRNA engineering:** The redundancy in the genetic code allows for a large number of mRNA sequences that encode the same protein. mRNA sequence may impact translation, thereby impacting the amount of protein produced in circulation. We are developing AI tools to predict mRNA sequences that can enhance protein expression.
- **Automated Sanger sequencing analysis:** Sanger sequencing is used repeatedly to quality check (QC) our DNA templates and final mRNA; while the data contain every nucleotide in a sequence, it is very complex to analyze. A fully automated data pipeline starts processing raw data the moment it is saved to the cloud by the sequencers. The pipeline spawns numerous AWS computer servers to run an analysis algorithm and then shuts the servers down, minimizing costs. The results are viewable in a powerful, dynamic visualization tool. We have run over three million Sanger data files through this system. We have further improved our Sanger analysis with a convolutional neural network (CNN) to better analyze the tail sections of mRNA as well.

Digital technologies to enable our clinical trials

We have deployed multiple digital technologies to drive the rapid pace of advancement, in parallel, of our development candidates into the clinic.

Digital systems for cGMP manufacture: We are committed to having integrated systems connected with robotics to drive our manufacturing in a paperless environment, and have designed and deployed automation to drive efficient manufacturing operations. We have also deployed digital tools within manufacturing process development that give us the ability to track, analyze, and rapidly deploy manufacturing process improvements. Additionally, we have implemented several digital systems across manufacturing process development, quality, supply chain, and operations, including:

- enterprise Quality Management System (QMS) to electronically manage deviations, investigation, and correction and preventive actions;
- Laboratory Information Management System (LIMS) to manage our analytical development data and automate our manufacturing quality control;
- computerized maintenance management system to manage equipment maintenance and calibration; and
- SAP/S4 Hana system for enterprise resource planning (ERP), manufacturing execution system, and manufacturing control system to manage inventories, track raw material consumption, digitally integrate equipment with manufacturing recipes in batch records, and control automated equipment.

Digital systems for clinical development and clinical operations: In order to track the timelines of various development candidates, we have created a set of integrated applications. Workflows include timelines for regulatory filings, planning for IND-enabling GLP toxicology studies, scheduling for cGMP manufacturing, and clinical operations management. Below is a summary of our applications:

- Our portfolio application is a digital interface that maintains and tracks the timelines across multiple workstreams for each of our development candidates.
- The supply application manages the manufacturing schedule of IND-enabling GLP toxicology supplies and cGMP manufacture of clinical supplies to support our programs. This application helps us see how the manufacturing schedule changes over time, identifies supply/demand mismatches, and enables resource planning with real-time alerts should we have any issues.
- The GLP toxicology application tracks the planned and ongoing IND-enabling GLP toxicology studies and allows us to manage timelines with our external vendors.
- The regulatory application tracks timelines related to regulatory affairs including, pre-IND meetings, IND/CTA submission dates, and other planned regulatory interactions.
- Our clinical operations application allows us to track our ongoing trials by accessing clinical operations information in real-time from our CROs. It also has multiple tools and analytics to draw key insights, including, for example, enrollment by trial and enrollment by site to maintain our program timelines.

Digital systems for PCV: The PCV program aims to design, manufacture, and deliver a drug product that includes an mRNA sequence encoding for each patient's specific neoantigens. The personalized nature of the PCV program adds additional steps and complexity in the overall patient treatment process. We have addressed those additional steps and complexity by digitizing and automating steps within the process, as described below.

- Each patient is provided a unique identifier. We track the entire workflow using a single integrated tracker based on this unique identifier. This is one of many ways we ensure that each patient receives the specific drug product lot manufactured for them.
- We use neural networks to design the mRNA sequences for the PCV program. Our proprietary vaccine design algorithm selects the top twenty neoantigens to be used and determines their amino acid sequences to trigger the desired immune response.
- We utilize Monte Carlo simulations of PCV supply/demand to manage our capacity. Since each drug product lot is personalized to a patient, there is a need to manage supply and demand to avoid bottlenecks at any stage of the workflow.

Digital systems for commercialization: Our investment in our digital capabilities prepared us to rapidly scale our production of our COVID-19 vaccine in 2021 and 2022. We are continuing to build out our commercial capabilities to establish medical affairs engagements with doctors, support our sales and marketing capabilities and deliver a world-class patient experience. In addition to a patient- and doctor-centric view, our commercial capabilities will strengthen our supply chain demand forecasting and our compliance. We are looking at building a robust serialization process for regulatory requirements as well as anti-counterfeiting technologies to ensure safe, efficacious medicines to patients.

Digital technologies to support our business processes

We have deployed several digital systems across finance, manufacturing, and human resources to automate our business processes and drive efficiencies. We have implemented the SAP S4/Hana system for ERP. We have implemented various cloud-based solutions to improve business processes and drive efficiencies. For example, we have implemented the Workday system for human resource planning and management and integrated various applications across payroll, 401(k) services, equity plan management and expense reporting. Our class-leading integration platform, Dell Boomi, allows us to have a highly interconnected environment, moving us from simple cloud-to-cloud integrations to an evolving use of the integration platform for master data management, systems account management, and ultimately for cost savings and improved user experience.

COMMERCIAL

We have grown our U.S. and international commercial sales organization beginning in early 2020 as we prepared for the commercialization of our COVID-19 vaccine. We have active commercial subsidiaries in 11 countries, including the U.S., Canada, many European countries and the Asia Pacific region, providing us with local commercial teams in key markets around the world. This commercial presence is supported by the Moderna International Business Service center in Warsaw, Poland. Our commercial teams also work in conjunction with third-party distributors and other partners in countries where we do not have a presence. In February 2022, we announced our intention to establish a commercial presence in six additional markets in Europe and four additional markets in Asia.

To date, our COVID-19 vaccine has been sold to government customers and international purchasing organizations, such as Gavi, on behalf of the COVAX Facility, and the African Union. We anticipate that most of our COVID-19 vaccine sales in 2022 will continue

to be pursuant to government contracts and these international purchasing organizations. We expect future sales to private customers if and as we gain marketing approval in various jurisdictions.

In addition, during 2021, we announced agreements in principle with the Canadian and Australian governments to establish mRNA manufacturing facilities in those countries, pursuant to which we would enter into long-term supply agreements for mRNA vaccines. See “Manufacturing” above for further detail.

THIRD-PARTY STRATEGIC ALLIANCES

Strategic alliances

To accelerate the discovery and advancement of potential mRNA medicines across therapeutic areas, we have entered into, and intend to seek other opportunities to form, alliances with a diverse group of strategic collaborators. We have forged productive strategic alliances with pharmaceutical and biotechnology companies, government agencies, academic laboratories, foundations and research institutes with therapeutic area expertise and resources. Through our collaborations, we seek to advance our discovery and development programs, while leveraging our platform and our research and early development capabilities. We also seek to partner with and invest in companies developing other types of therapeutics, such as gene editing and cell-therapy, where we believe we can leverage our core mRNA and LNP capabilities to expand the reach of our technology.

Through certain of our strategic alliances, we share the rewards and risks of developing a new mRNA modality or program, where we may have early research data and desire a strategic collaborator to join us in advancing early development candidates within such modality into the clinic. Representative relationships and associated programs include those with:

- **AstraZeneca** for the VEGF-A program (AZD8601) in the localized regenerative therapeutics modality, and the IL-12 program (MEDI1191) in the intratumoral immuno-oncology modality;
- **Merck** for the personalized cancer vaccine program (mRNA-4157) in the cancer vaccines modality; and
- **Vertex** for the cystic fibrosis (CF) program (VXc-522) in the inhaled pulmonary therapeutics modality.

We view strategic alliances as important drivers for accelerating execution of our goal of rapidly developing mRNA medicines to treat patients across a wide range of medical and disease challenges. To maintain the integrity of our platform, the terms of our agreements with our strategic collaborators generally provide that either we receive rights to develop and commercialize potential mRNA medicines that we design and manufacture or our strategic collaborators receive rights to develop and commercialize potential mRNA medicines that we design and manufacture, as opposed to granting rights to our strategic collaborators to use our platform to generate new mRNA technologies, and that we generally own mRNA-related intellectual property arising from research activities performed under the strategic alliance. We plan to continue to identify potential strategic collaborators who can contribute meaningful technology and insights to our programs and allow us to more rapidly expand our impact to broader patient populations.

Below are brief descriptions of certain of our collaborations. For additional information on these relationships, including their ongoing financial and accounting impact on our business, please see *Note 5, Collaboration Agreements*, to our consolidated financial statements included in this Annual Report on Form 10-K.

AstraZeneca (Nasdaq: AZN)—Strategic Alliances in Cardiovascular and Oncology

We have two ongoing strategic alliances with AstraZeneca. Pursuant to the first collaboration, which was established in 2013 and amended and restated in 2018, we granted AstraZeneca certain exclusive rights and licenses to research, develop and commercialize potential mRNA medicines directed at certain targets for the treatment of cardiovascular and cardiometabolic diseases and cancer, and agreed to provide related services to AstraZeneca. Our localized VEGF-A program (AZD8601) is being developed by AstraZeneca pursuant to this alliance.

Pursuant to our second strategic alliance with AstraZeneca, which was established in 2016, we agreed to collaborate to discover, develop and commercialize potential mRNA medicines in a range of cancers. We and AstraZeneca have agreed to work together on an immune-oncology program focused on the intratumoral delivery of a potential mRNA medicine to make the IL-12 protein, and our IL-12 program (MEDI1191) is being developed in collaboration with AstraZeneca pursuant to this alliance.

Merck (NYSE: MRK)—Strategic Alliances in Infectious Diseases and Cancer Vaccines

We have established a multi-faceted relationship with Merck Sharp & Dohme Corp. (Merck) that includes distinct strategic alliances directed to the research, development, and commercialization of mRNA medicines for the prevention and treatment of viral infections and for the treatment of cancer.

2016 Cancer Vaccine Strategic Alliance—Personalized mRNA Cancer Vaccines with Merck

In June 2016, we entered into a personalized mRNA cancer vaccines (PCV) Collaboration and License Agreement with Merck (PCV Agreement) to develop and commercialize PCVs for individual patients using our mRNA vaccine and formulation technology. Under the strategic alliance, we identify genetic mutations present in a particular patient's tumor cells, synthesize mRNA for these mutations, encapsulate the mRNA in one of our proprietary LNPs and administer to each patient a unique mRNA cancer vaccine designed to specifically activate the patient's immune system against her or his own cancer cells.

Pursuant to the PCV Agreement, we are responsible for designing and researching PCVs, providing manufacturing capacity and manufacturing PCVs, and conducting Phase 1 and Phase 2 clinical trials for PCVs, alone and in combination with KEYTRUDA (pembrolizumab), Merck's anti-PD-1 therapy, all in accordance with an agreed upon development plan and budget.

2018 Expansion of the Cancer Vaccine Strategic Alliance with Merck—Shared Neoepitope Cancer Vaccines

In April 2018, we and Merck agreed to expand our cancer vaccine strategic alliance to include the development and commercialization of our KRAS vaccine development candidate, mRNA-5671, and potentially other shared neoantigen mRNA cancer vaccines (SAVs). We preclinically developed mRNA-5671 prior to its inclusion in the cancer vaccine strategic alliance and it is comprised of a novel mRNA construct designed by us and encapsulated in one of our proprietary LNPs. The PCV Agreement was amended and restated to include the new SAV strategic alliance (PCV/SAV Agreement). We have regained all rights to our KRAS vaccine (mRNA-5671) from Merck and we are evaluating next steps for the program.

Vertex (Nasdaq: VRTX)—2016 Strategic Alliance in Cystic Fibrosis

In July 2016, we entered into a Strategic Collaboration and License Agreement (Vertex Agreement) with Vertex Pharmaceuticals Incorporated, and Vertex Pharmaceuticals (Europe) Limited (together, Vertex). The Vertex Agreement is aimed at the discovery and development of potential mRNA medicines for the treatment of cystic fibrosis (CF) by enabling cells in the lungs of people with CF to produce functional cystic fibrosis transmembrane conductance regulator (CFTR) proteins.

Vertex—2020 Strategic Alliance in Cystic Fibrosis

In September 2020, we entered into a new Strategic Collaboration and License Agreement with Vertex (Vertex 2020 Agreement). The Vertex 2020 Agreement is aimed at the discovery and development of potential medicines to treat CF by delivering gene-editing therapies to lung cells to facilitate production of functional CFTR proteins.

The three-year research period of the Vertex 2020 Agreement will initially focus on the identification and optimization of novel LNPs and mRNAs that can deliver gene-editing therapies to cells in the lungs. Following the initial three-year period, Vertex is responsible for conducting development and commercialization activities for candidates and products that arise from the strategic alliance, including the costs associated with such activities. Vertex is also obligated to pay us for research services in connection with our performance of certain activities in accordance with a jointly agreed research plan. Subject to customary "back-up" supply rights granted to Vertex, under the agreement, we are the exclusive manufacturer of related mRNA and LNPs for preclinical, clinical, and commercialization purposes.

Other Collaborations

Chiesi—2020 Collaboration and License Agreement with Chiesi

In September 2020, we entered into a Collaboration and License Agreement (Chiesi Agreement) with Chiesi Farmaceutici S.P.A. (Chiesi). The Chiesi Agreement is aimed at the discovery and development of potential mRNA medicines for the treatment of pulmonary arterial hypertension (PAH), a rare disease characterized by high blood pressure in the arteries of the lungs.

Metagenomi—2021 Collaboration for Next-Generation In Vivo Gene Editing Therapeutics

In November 2021, we entered into a strategic research and development collaboration with Metagenomi, Inc. (Metagenomi) focused on advancing new gene editing systems for *in vivo* human therapeutic applications. The collaboration intends to utilize Metagenomi's novel gene editing tools and leverage our mRNA platform, as well as LNP delivery technologies, with the goal of developing curative therapies for patients with serious genetic diseases. Under the terms of the collaboration, we and Metagenomi have agreed to advance a series of *in vivo* gene editing therapeutics against undisclosed targets. We agreed to pay Metagenomi an up-front cash payment and make an equity investment in Metagenomi in the form of a convertible note. Metagenomi is eligible to receive certain target option exercise fees as well as certain milestone payments, plus tiered royalties on net sales of any products that are commercialized by us under the agreement.

Carisma Therapeutics—2022 Collaboration For In Vivo CAR-M Therapeutics

In January 2022, we entered into a new strategic collaboration agreement with Carisma Therapeutics, Inc. (Carisma) to discover, develop and commercialize *in vivo* engineered chimeric antigen receptor monocyte (CAR-M) therapeutics for the treatment of cancer, including solid tumors. Under the terms of the agreement, we agreed to pay Carisma an up-front cash payment and make an equity investment in Carisma in the form of a convertible note. Carisma will receive research funding and is eligible to receive certain milestone payments, plus tiered royalties on net sales of any products that are commercialized by us under the agreement. Carisma will be responsible for the discovery and optimization of development candidates while we will lead the clinical development and commercialization of therapeutics resulting from the agreement. We have the option to nominate up to twelve targets for development and commercialization.

Strategic alliances with government organizations and foundations

Defense Advanced Research Projects Agency (DARPA)

In October 2013, DARPA awarded us up to approximately \$25 million under Agreement No. W911NF-13-1-0417 to research and develop potential mRNA medicines as a part of DARPA's Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) program, which is focused on assisting with the development of technologies to rapidly identify and respond to threats posed by natural and engineered diseases and toxins. As of December 31, 2021, \$20 million of the award amount has been funded. This award followed an initial award from DARPA given in March 2013 under Agreement No. W31P4Q-13-1-0007. The DARPA awards have been deployed primarily in support of our vaccine and antibody programs to protect against Chikungunya infection. Although our antibody against Chikungunya virus (mRNA-1944) had positive Phase 1 readouts, we do not have plans to advance to a Phase 2 study.

In September 2020, we entered into an agreement with DARPA for an award of up to \$56 million to fund development of a mobile manufacturing prototype leveraging our existing manufacturing technology that is capable of rapidly producing vaccines and therapeutics. As of December 31, 2021, the committed funding, net of revenue earned was \$2 million, with an additional \$42 million available under Agreement No. HR0011-20-9-0118 if DARPA exercises additional contract options.

Biomedical Advanced Research and Development Authority (BARDA)

In September 2016, we received an award of up to approximately \$126 million under Agreement No. HHSO100201600029C from BARDA, a component of the Office of the Assistant Secretary for Preparedness and Response (ASPR), within the U.S. Department of Health and Human Services (HHS), to help fund our Zika vaccine program. Under the terms of the agreement with BARDA, an initial base award of approximately \$8 million supported toxicology studies, a Phase 1 clinical trial, and associated manufacturing activities. Additionally, four contract options were awarded under the agreement with BARDA. Three out of four of these options have been exercised, bringing the total current award to approximately \$117 million to support an additional Phase 1 study of an improved Zika vaccine candidate, Phase 2 and Phase 3 clinical studies, as well as large-scale manufacturing for the Zika vaccine.

In April 2020, we entered into an agreement with BARDA for an award of up to \$483 million to accelerate development of mRNA-1273, our COVID-19 vaccine. In July 2020, we amended our agreement with BARDA to provide for an additional commitment of up to \$472 million to support late-stage clinical development of mRNA-1273, including the execution of a 30,000 participant Phase 3 study in the U.S. We further amended the agreement in March 2021 to provide for an additional commitment of \$63 million to further support late-stage clinical development, including Phase 2/3 mRNA-1273 pediatric studies. In April 2021, we entered into a further amendment to the BARDA agreement, increasing the amount of potential reimbursements by \$236 million in connection with costs associated with the Phase 3 clinical trials for mRNA-1273 and pharmacovigilance efforts. In June 2021, the agreement was further amended to award additional funding of \$144 million to support pediatric clinical trials for mRNA-1273. The maximum award from BARDA, inclusive of the 2020 and 2021 amendments, is \$1.4 billion. Under the terms of the agreement, BARDA will fund the advancement of mRNA-1273 to FDA licensure. All contract options have been exercised. As of December 31, 2021, the remaining available funding net of revenue earned was \$189 million.

Institute for Life Changing Medicines (ILCM)

In September 2021, we entered into a collaboration agreement with the ILCM to develop a new mRNA therapeutic (mRNA-3351) for CN-1. Under the terms of the agreement, we agreed to license mRNA-3351 to ILCM with no upfront fees, and without any downstream payments. ILCM will be responsible for the clinical development of mRNA-3351.

The Bill & Melinda Gates Foundation

In January 2016, we entered a global health project framework agreement with the Bill & Melinda Gates Foundation to advance mRNA-based development projects for various infectious diseases. The Bill & Melinda Gates Foundation has committed up to \$20 million in grant funding to support our initial project related to the evaluation of antibody combinations in a preclinical setting as well as the conduct of a first-in-human Phase 1 clinical trial of a potential mRNA medicine to help prevent HIV infections. Follow-on projects, which could bring total potential funding under the framework agreement up to \$100 million (including the HIV antibody project) to support the development of additional mRNA-based projects for various infectious diseases, can be proposed and approved until the sixth anniversary of the framework agreement, subject to the terms of the framework agreement, including our obligation to grant to the Bill & Melinda Gates Foundation certain non-exclusive licenses.

INTELLECTUAL PROPERTY

We rely on a combination of intellectual property laws, including patent, trademark, copyright and trade secret, as well as confidentiality and license agreements, to protect our intellectual property and proprietary rights.

Protecting our platform, modality, and program investments: Building an expansive, multi-layered IP estate

We have built a substantial IP estate that includes numerous patents and patent applications related to the development and commercialization of mRNA vaccine and therapeutic development candidates, including related platform technologies. Our platform IP protects advances in mRNA design and engineering, proprietary LNP components, delivery systems, processes for the manufacture and purification of drug substances and products, and analytical methods. A significant portion of our platform IP estate further provides multi-layered protection for our modalities and programs.

With respect to our IP estate, our solely-owned patent portfolio consists of more than 170 issued or allowed U.S. patents or patent applications and more than 110 granted or allowed patents in jurisdictions outside of the U.S. (including granted European patents that have been validated in numerous European countries) covering certain of our proprietary platform technology, inventions, and improvements, and covering key aspects of our clinical and most advanced development candidates. We have over 430 additional pending patent applications that, in many cases, are counterparts to the foregoing U.S. and foreign patents.

Most of the patents and applications (if issued) in our portfolio will not expire until 2033 at the earliest. Any patent that may issue from our most recently filed patent applications is projected to expire between 2042 and 2043, at the earliest. We file additional U.S. and foreign patent applications as necessary to protect our evolving intellectual property position.

We also rely on trademarks, copyright, trade secrets, and know-how relating to our proprietary technology and programs, continuing innovation, and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of mRNA therapeutic and vaccine technologies. We take additional steps, such as entering into confidentiality and license agreements, to protect our intellectual property and proprietary rights. We additionally plan to rely on data exclusivity, market exclusivity, and patent term extensions when available, and plan to seek and rely on regulatory protection afforded through orphan drug designations. We also possess substantial proprietary know-how associated with related manufacturing processes and expertise.

IP protecting our platform

We have a broad IP estate covering key aspects of our platform. This estate provides multiple layers of protection covering the making and use of the mRNA drug substance and delivery technologies.

With respect to our platform, we have a portfolio that includes U.S. and foreign patents or patent applications covering platform innovations that are directly related to the design, formulation and manufacturing of mRNA medicines. For example, these patents and patent applications include claims directed to:

- mRNA chemistry imparting improved properties for vaccine and therapeutic uses;
- methods for mRNA sequence optimization to enhance the levels and fidelity of proteins expressed from our mRNA medicines;
- methods for identifying epitopes having superior suitability in cancer vaccine contexts;
- engineering elements tailored to enhance stability and the *in vivo* performance of mRNA medicines;
- LNP delivery systems, including novel lipid components designed for optimal expression of both therapeutic and vaccine mRNAs, in particular, prophylactic infectious disease and cancer vaccine mRNAs, intratumoral immuno-oncology therapeutics, local regenerative therapeutics, systemic therapeutics, and inhaled pulmonary therapeutics; and
- innovative processes for the manufacture and analysis of mRNA drug substance and formulated drug product.

IP protection for modalities

Our IP estate provides protection for the multiple programs within our modalities both at the product-specific level and at various broader levels. For example, we have patent coverage for LNP-encapsulated mRNAs having specific chemical modification suited for vaccine and therapeutic mRNA use. Our estate also includes IP covering certain LNP-encapsulated mRNAs coding for infectious disease antigens for use in prophylactic vaccination. Our mRNA chemistry, formulation and manufacturing patent applications and related know-how and trade secrets may also provide us with additional IP protection relating to our development candidates.

Prophylactic vaccines

For programs within our prophylactic vaccines modality, we typically pursue patent protection featuring composition of matter and method of use claims. Our global patent protection strategy may vary based on the unique geographic prevalence of various infectious diseases.

We have filed several patent applications covering our COVID-19 vaccine program. Claims covering mRNA-1273, which is a LNP-encapsulated mRNA encoding prefusion-stabilized Spike protein antigen, and claims to methods of vaccinating subjects against SARS-CoV-2 infection using our vaccine are featured in several patent families that includes four pending PCT applications, a pending U.S. patent application, and foreign patent applications filed in Argentina and Taiwan. Priority dates for these applications span a period from late January through late May 2020. The U.S. government has rights in certain of the foregoing patent applications. A further pending PCT application includes claims covering our variant-specific COVID-19 vaccines. Protection for mRNA-1283 can be found in a PCT application and three pending U.S. provisional patent applications. Two additional U.S. provisional patent applications include claims covering our COVID-19 and seasonal flu combination vaccine.

Issued U.S. Patent No. 10,702,600 includes claims to LNP-encapsulated mRNA encoding betacoronavirus spike protein. Issued U.S. patent 10,933,127 includes claims to methods of using such compositions to elicit an immune response in subjects. Corresponding vaccine composition and method of use claims are also featured in a pending European patent application. These patents and applications enjoy an October 2015 priority date.

Further coverage for our COVID-19 vaccine and many of our other prophylactic vaccines is found in a broad, infectious disease vaccine patent family featuring claims to LNP-encapsulated mRNAs encoding infectious disease antigens and methods using such compositions for vaccination. This patent family includes two issued U.S. patents, two pending U.S. patent applications and pending patent applications in Europe, Canada, Australia, Brazil, China, Hong Kong, India, Japan, Russia, and Singapore. Issued U.S. Patent Nos. 10,022,435 and 10,709,779 feature claims directed to methods of vaccinating subjects against infection with LNP-encapsulated mRNAs encoding infectious disease antigens.

Patent coverage for our human CMV vaccine, which includes mRNAs encoding several surface glycoproteins of the CMV virus, can be found in pending applications in Australia, Canada, Europe and in both a granted patent and pending patent application in Japan. In the United States, our CMV vaccine is covered in a pending U.S. patent application and in issued U.S. Patent Nos. 10,064,935, 10,383,937 and 10,716,846. Two pending PCT applications and a pending U.S. patent application feature claims to clinical formulations of our CMV vaccine and methods of use.

Patent applications directed to our hMPV/PIV3 vaccine are pending in the United States, Europe and Hong Kong. Five U.S. patents have issued featuring hMPV/PIV3 vaccines with U.S. Patent No. 10,064,934 having claims covering LNP-encapsulated mRNA vaccines that encode the PIV3 and hMPV fusion proteins, U.S. Patent No. 10,272,150 having claims covering administration methods for these LNP-encapsulated mRNA vaccines, U.S. Patent No. 10,543,269 having claims covering vaccines that include HMPV-encoding mRNA formulated in LNPs, U.S. Patent No. 10,702,599 having claims covering vaccines that include PIV3-encoding mRNA formulated in LNPs, and U.S. Patent 11,103,578 having claims covering specific HMPV- and PIV3-encoding mRNAs for use as vaccines. A pending provisional patent application features claims to clinical aspects of our hMPV/PIV3 vaccine. A pending U.S. patent application features claims covering our hMPV/RSV vaccine.

Our Zika mRNA vaccine is covered in a series of patent families directed to mosquito-borne viruses. These patent families include four issued U.S. Patents that cover our Zika vaccines, U.S. Patent Nos. 10,449,244, 10,653,767, 11,007,260 and 11,207,398, and several pending U.S., European and Hong Kong patent applications, one of which is recently allowed and soon to be issued as a U.S. patent, and one of which is recently allowed and soon to be granted as a European patent.

We filed patent applications in several jurisdictions covering RSV vaccines. At least two U.S. and two European patent applications are pending, as are applications in Canada, Australia and several Asian jurisdictions. Also pending are two provisional applications featuring our pediatric RSV vaccine.

A pending PCT patent application and a pending U.S. provisional patent application includes claims covering our vaccine program for the prevention of human infection with seasonal influenza virus. The program also is protected by the broad, infectious disease

vaccine patent family described above, in particular, issued U.S. Patent No. 9,872,900 and granted European Patent EP 3134131, having claims to HA-encoding mRNA vaccine compositions.

Pending patent applications in the United States, Australia, Canada, Europe, and Japan include claims covering our EBV vaccines and methods of use.

We have pending patent applications in the United States and Europe that include claims covering our Nipah vaccine and methods of use, and pending applications in the United States and Europe that include claims covering our HIV vaccine and methods of use.

Cancer vaccines

Composition of matter and method claims also protect programs within our cancer vaccines modality. Proprietary methods around the making and therapeutic use of our personalized cancer vaccines (PCVs) and resulting vaccine compositions are described and claimed in six pending U.S. patent applications, five pending European patent applications, four pending patent applications in each of Australia, Canada, China and Japan, and several pending patent applications in New Zealand, South Africa, as well as other European, Asian and South American countries. Of these patent applications, a U.S. patent application and a Chinese patent application are allowed and soon to be issued. These applications also relate to various vaccine design formats, in particular, polyepitopic vaccine formats, and methods of treating cancer with such personalized cancer vaccines. We also possess substantial know-how and trade secrets relating to the development and commercialization of our cancer vaccine programs, including related manufacturing process and technology.

Likewise, our KRAS antigen cancer vaccine and methods of treating cancer featuring such vaccines are covered in issued U.S. Patent No. 10,881,730, which includes claims to LNP-encapsulated mRNA encoding mutant KRAS antigens, and in a pending U.S. patent application and pending applications in Australia, Canada, Europe, and Japan, as well as in several other European, South American, Asian and Middle Eastern jurisdictions.

Intratumoral immuno-oncology

To protect programs within our intratumoral immuno-oncology modality, we have filed numerous patent applications featuring claims to mRNAs encoding immune-stimulatory proteins and methods of treating cancer using such compositions.

Two of our immuno-oncology programs are designed to be administered intratumorally to alter the tumor microenvironment in favor of mounting an immune response against tumors. Our mRNA program that includes mRNAs that encode OX40L, IL-23 and IL-36 γ are covered by a granted European Patent, EP 3394093, by eleven issued U.S. patents, U.S. Patent Nos. 10,143,723, 10,172,808, 10,285,950, 10,322,090, 10,322,091, 10,379,767, 10,383,951, 10,406,113, 11,003,366, 11,071,716 and 11,185,510, by several pending U.S. and European patent applications, two of which are allowed and soon to issue, and by several pending patent applications in foreign jurisdictions including Asian, South American and other jurisdictions. These applications feature claims to the mRNA therapeutics as compositions of matter, formulations that include such mRNAs and methods of reducing tumors and treating cancer featuring these development candidates. Similar claims cover our IL-12 development candidate which can be found in issued U.S. Patent No. 10,646,549, issued U.S. Patent No. 11,000,573, and in pending patent applications in the United States and Europe, two of which are allowed and soon to be issued, and in Australia, Canada, China and Japan, as well as several other jurisdictions in Asia, South America and the Middle East.

Localized regenerative therapeutics

Our localized regenerative therapeutics modality is focused on regenerative therapeutics. Our sole program, VEGF-A, is being developed in collaboration with AstraZeneca and is covered by a granted European patent EP 3464338, granted Japanese patent JP 6859369 and granted Russian patent RU 2756313, and by pending U.S. and European patent applications and by several national phase patent applications filed in South American, Asian and Middle Eastern jurisdictions. The VEGF patent applications are solely-owned by Moderna.

Systemic intracellular therapeutics

Within our systemic intracellular therapeutics modality, we have four programs featuring expression of intracellular enzymes for the treatment of rare diseases. For our rare disease programs, we generally pursue patent protection featuring composition of matter and method of use claims, for example, pharmaceutical composition and method of treatment claims. Our most advanced rare disease development candidate, MMA, is covered by a patent family that includes issued U.S. Patent No. 10,406,112, two pending U.S. patent applications, foreign patent applications filed in Australia, Canada, Japan, Europe and the Middle East, and two pending U.S. Provisional patent applications.

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For our PA development candidate, we have patent applications pending in the United States, Canada, Europe, and Japan which cover mRNA encoding the alpha and beta subunits of the enzyme propionyl-CoA carboxylase (PCCA and PCCB, respectively), for the treatment of PA.

For our PKU development candidate, we have a pending PCT and pending patent applications in the U.S., Europe and Japan covering mRNA encoding phenylalanine hydroxylase (PAH) for the treatment of PKU.

For our Glycogen Storage Disorder, Type 1a (GSD1a) development candidate, we have pending U.S and European patent applications, as well as applications pending in Australia, Canada, China, Japan, Israel and several Middle Eastern jurisdictions, and a pending PCT and pending provisional patent applications covering mRNA encoding glucose 6-phosphatase (G6Pase) for the treatment of this disorder.

For our Crigler-Najjar Syndrome Type 1 (CN-1) development candidate, we have patent applications pending in the U.S., Europe, Australia, Canada and Japan.

Any U.S. and foreign patents that may issue from these patent families would be expected to expire in 2036 for the earliest of the MMA patents and 2038-2042 for the remaining MMA, PA, PKU, GSD1a and CN-1 patents, excluding any patent term adjustments and any patent term extensions.

As further described below, we have filed or intend to file patent applications on these and other aspects of our technology and development candidates, and as we continue the development of our intended products, we plan to identify additional means of obtaining patent protection that would potentially enhance commercial success, including protection for additional methods of use, formulation, or manufacture.

Systemic secreted and cell-surface therapeutics

Our systemic secreted and cell-surface therapeutics modality features programs directed to expression of secreted or cell-surface proteins including antibodies, circulating modulation factors, secreted enzymes and transmembrane proteins. Our mRNA-encoded antibody against Chikungunya virus reported positive interim Phase 1 results in clinical trials and utilizes the same LNP formulation being advanced for our MMA program and other rare disease programs. Patent protection for mRNA-encoded antibody against Chikungunya virus is being sought by way of a pending U.S. and European patent applications, in which we share joint ownership rights.

Our Relaxin development candidate is covered by several pending foreign patent applications outside the United States, for example, in several Asian, European, Middle Eastern, South American and other jurisdictions, and by a pending U.S. application and by issued U.S. Patent No. 10,730,924.

Our PD-L1 and IL-2 development candidates are each covered in pending PCT patent applications.

Inhaled pulmonary therapeutics

Our inhaled pulmonary therapeutics modality currently has one development candidate directed to expression of therapeutic protein in the lungs. This Cystic Fibrosis (CF) development candidate is covered by pending U.S., European and PCT patent applications.

Trademarks

Our trademark portfolio currently contains at least 200 trademark registrations, including at least 12 registrations in the United States and the remaining in Canada, the European Union, the United Kingdom, Israel, China, Japan, Australia, and elsewhere. In addition, we have at least 375 pending trademark applications in more than 75 jurisdictions, including in the aforementioned locations and additional countries throughout Africa, Asia, and South America.

In-licensed intellectual property

While we develop and manufacture our potential mRNA medicines using our internally created mRNA technology platform, we also seek out and evaluate third party technologies and IP that may be complementary to our platform.

Patent sublicense agreements with Cellscript and mRNA RiboTherapeutics

The Trustees of the University of Pennsylvania owns several issued U.S. patents, granted European patents and pending U.S. patent applications directed, in part, to nucleoside-modified mRNAs and their uses, or the Penn Modified mRNA Patents. mRNA

RiboTherapeutics, Inc. (MRT) obtained an exclusive license to the Penn Modified mRNA Patents and granted its affiliate, Cellscript, LLC (Cellscript), a sublicense to the Penn Modified mRNA Patents in certain fields of use.

In June 2017, we entered into two sublicense agreements, one with Cellscript, and one with MRT, which agreements we collectively refer to as the Cellscript-MRT Agreements. Together, the Cellscript-MRT Agreements grant us a worldwide, sublicensable sublicense to the Penn Modified mRNA Patents to research, develop, make, and commercialize products covered by the Penn Modified mRNA Patents, or licensed products, for all *in vivo* uses in humans and animals, including therapeutic, prophylactic, and diagnostic applications. The Cellscript-MRT Agreements are non-exclusive, although Cellscript and MRT are subject to certain time restrictions on granting additional sublicenses for *in vivo* uses in humans under the Penn Modified mRNA Patents.

We paid Cellscript and MRT aggregate sublicense grant fees of \$28 million upon entering into the Cellscript-MRT Agreements, \$25 million in early 2018, and \$22 million in early 2019. Cellscript and MRT are collectively eligible to receive, on a licensed product-by-licensed product basis, milestone payments totaling up to \$0.5 million upon the achievement of certain regulatory-based events for diagnostic products, and milestone payments totaling up to \$1.5 million upon the achievement of certain development and regulatory-based events for either therapeutic or prophylactic products, and up to \$24 million upon the achievement of certain commercial-based events for either therapeutic or prophylactic products. The Cellscript-MRT Agreements require us to pay royalties based on annual net sales of licensed products at rates in the low single digits for therapeutic, prophylactic, and diagnostic uses, and royalties based on annual net sales of licensed products sold for research uses at rates in the mid-single digits, subject to certain reductions, with an aggregate minimum floor. Following the first commercial sale of licensed products under a Cellscript-MRT Agreement, we are required to pay Cellscript or MRT, as applicable, minimum annual royalties ranging from \$10,000 to \$400,000 depending on the use of such licensed product, with all such payments creditable against earned royalties on net sales. In 2021, we paid \$641 million in royalties and milestone payments to Cellscript in connection with sales of our COVID-19 vaccine.

The Cellscript-MRT Agreements will terminate upon the expiration or abandonment of the last to expire or become abandoned of the Penn Modified mRNA Patents. Cellscript or MRT, as applicable, may terminate its respective Cellscript-MRT Agreement if we fail to make required payments or otherwise materially breach the applicable agreement, subject to specified notice and cure provisions. Cellscript or MRT, as applicable, may also terminate the applicable Cellscript-MRT Agreement upon written notice in the event of our bankruptcy or insolvency or if we challenge the validity or enforceability of the Penn Modified mRNA Patents. We have the right to terminate each Cellscript-MRT Agreement at will upon 60 days' prior notice to Cellscript or MRT, as applicable, provided that we cease all development and commercialization of licensed products upon such termination. If rights to MRT or Cellscript under the Penn Modified mRNA Patents are terminated (e.g., due to bankruptcy of MRT or Cellscript), the terminated party will assign its interest in the respective Cellscript-MRT Agreement to the licensor from which it received rights under the Penn Modified mRNA Patents and our rights will continue under the new licensor.

Formulation technology in-licenses

Our development candidates use internally developed formulation technology that we own. We do, however, have rights to use and exploit multiple issued and pending patents covering formulation technologies under licenses from other entities. If in the future we elect to use or to grant our strategic collaborators sublicenses to use these in-licensed formulation technologies, we or our strategic collaborators may be liable for milestone and royalty payment obligations arising from such use. We consider the commercial terms of these licenses and their provisions regarding diligence, insurance, indemnification and other similar matters, to be reasonable and customary for our industry.

HUMAN CAPITAL

We had approximately 2,700 full-time employees as of December 31, 2021, representing a more than doubling of our workforce from 1,300 full-time employees as of the end of the prior year. We have undertaken significant hiring of employees to facilitate manufacturing of our COVID-19 vaccine, in addition to building out our commercial and regulatory organizations, as well as other functions, to support this continued roll-out. We also increased our hiring outside the United States during 2021, and at year-end we had employees in 12 countries around the world, with a presence in North America, Europe and the Asia-Pacific region. Much of this hiring has been of talent with experience at other pharmaceutical companies as we continue to build out our commercial and regulatory capabilities, particularly as we fill roles to facilitate our operations and commercial activities in markets around the globe. We have also continued to hire talent to support our research and clinical capabilities across the rest of our pipeline, unrelated to our COVID-19 vaccine.

We operate in a highly competitive environment for human capital, particularly as we seek to attract and retain talent with experience in the biotechnology and pharmaceutical sectors. Our workforce is highly educated, and as of December 31, 2021, 47% of our employees hold Ph.D., Doctorate, M.D., J.D., or Master's degrees. Among our employees, as of December 31, 2021, 47% are female. Among our leadership (which we define as employees at the vice president level and above), as of December 31, 2021, approximately 39% are female, an increase from 37% in the prior year. 40% of our U.S. employees identify as racially or ethnically diverse as of

December 31, 2021, an increase from 35% in the prior year. In 2021, we continued to act on our commitment to belonging, inclusion & diversity by, among other things:

- engaging all members of our Executive Committee, vice presidents and managers in our Conscious Inclusion education series;
- conducting diversity-related events, celebrations and learning opportunities for all employees throughout the year, including Pride Month, Hispanic Heritage Month and Asian & Pacific Islander Month;
- hosting a company-wide event on Neurodiversity in line with the CEO Action of Diversity & Inclusion's #DayofUnderstanding;
- increased our monitoring and reporting program regarding company-wide gender and ethnicity data;
- doubling the number of our Employee Resource Groups; and
- joining the Disability:IN Inclusion Works Program, an initiative that assists employers in all aspects of disability inclusion at work.

To help promote alignment between our employees and our shareholders, all employees participate in our equity programs through the receipt of equity grants, and the percentage of equity as a component of overall pay mix increases with seniority. We believe that in addition to incentivizing growth that leads to shareholder value, broad eligibility for our equity programs helps promote employee retention as these awards generally vest over a four-year period.

Throughout the COVID-19 pandemic, we have implemented various initiatives to promote the safety of our workforce and continuity of our operations. We created a Coronavirus Response Team that is responsible for implementing various safety measures at our global sites. Our protocols include regular COVID-19 testing and the provision personal protective equipment (PPE). Throughout the pandemic, much of our workforce has worked remotely, wherever possible and when local conditions recommend social distancing. We also implemented remote hiring and onboarding programs to facilitate significant hiring during 2021 in a remote work environment.

Since October 2021, we have required all of our employees in the United States to be vaccinated against COVID-19, including having received a booster dose, absent an approved medical or religious accommodation. In December 2020, following the receipt of an Emergency Use Authorization from the FDA for our COVID-19 vaccine, we made the vaccine available to our employees and adult members of their households to help ensure continuity of our operations due to the critical nature of our production of the vaccine. In December 2021 and early 2022, as the Omicron variant drove a surge in COVID-19 cases globally, we made booster doses of our vaccine available to our U.S.-based employees and adult members of their households, as well as to employees of our Swiss subsidiary.

None of our employees are represented by a labor union, and none of our employees have entered into a collective bargaining agreement with us, other than a small number of employees in France, Italy and Spain who are covered by collective bargaining agreements governing certain benefits and working conditions. We consider our employee relations to be good.

We believe that our employees are highly engaged, and we and our employees have been recognized by surveys conducted by external groups. *Science* magazine ranked us as a top employer for each of the last seven years. Additionally, in 2021, *Biospace* ranked us the number one employer in its 2022 Best Places to Work in Biopharma report and *Fast Company* named us the number one company on its 2021 Best Workplaces for Innovators list. We measure employee engagement through a vendor-supplied engagement software, using validated external benchmarks to track quarter-over-quarter employee engagement factors.

Our approach to attracting and retaining talent

We are committed to ensuring that our employees find that their careers at Moderna are filled with purpose, growth and fulfillment. We believe that a career at Moderna provides opportunity for:

- **Impact:** Our people will have the opportunity to do work that is unparalleled in terms of its innovation and scope of impact on people's lives.
- **Growth:** We provide incredible opportunities for growth and we obsess over learning (as demonstrated, in part, by our Mindsets (see below)). We invest in the development of our people as scientists and as leaders.
- **Well-being:** We are committed to the health and well-being of our employees and their families by providing family-friendly benefits and opportunities to be healthy, including annual allowances for personal enrichment and monthly allowances for fitness and nutrition.
- **Inclusive environment:** We believe in the benefits of bringing together a diverse set of perspectives and backgrounds, and creating an environment where differences are celebrated and leveraged.
- **Compelling rewards:** To attract and retain the best talent, we provide competitive rewards that help to drive groundbreaking work and allow employees to share in the value we will create together, including through our equity programs.

Our approach to training our employees

We have established a structured training curriculum for our employees called Moderna University and have a full-time team dedicated to developing the curriculum and conducting activities for Moderna University. The objective of Moderna University is for every employee to be deeply familiar with our core technology and able to learn about technologies that might further enable our science. In addition, Moderna University is also focused on creating strong leaders through management and leadership training. There are four core areas within Moderna University including:

- **Professional development:** Includes on-site training programs for our employees including those focused on leadership and project management, as well as tools to improve interpersonal communication.
- **Digital learning library:** We have built an online library of videos of a variety of scientific material that our employees can access flexibly. This content includes:
 - Presentations by external speakers to scientific seminars conducted in-house;
 - Scientific courses at external universities; and
 - Peer-to-peer video series in which in-house experts provide an introductory view of complex topics they tackle within their teams.
- **Learning management system:** We have deployed a digital system to track and administer training programs for each of our employees. Training content is developed digitally and offered to our employees.
- **New hire orientation:** This program is designed to onboard all new employees. During this training program, new employees meet with members of the management team and senior functional leaders to learn about the Company and functional activities.

In December 2021, we announced the launch of our Artificial Intelligence (AI) Academy in partnership with Carnegie Mellon University. The AI Academy is intended to educate and empower our workforce to identify and integrate AI and machine learning solutions into our systems and processes.

Additionally, with the continued rapid growth of our company, we articulated the Moderna Mindsets in late 2021. The Moderna Mindsets are a set of leadership behaviors we use to make decisions and lead the company. We consider the Mindsets to be key as our company continues to scale, and we are working to integrate them into all of our HR processes, including performance management. Our employees participate in the Mindsets Workshops, which is an interactive, full-immersion learning experience designed to provide the opportunity to engage with, better understand and learn how to apply the Mindsets in the workplace.

To further develop and retain our workforce, we conduct periodic talent reviews that identify key talent within the organization. We use that data to inform specific development opportunities for key current and potential future leaders, and to support our periodic succession planning activities for key roles. These steps together ensure we have a robust understanding of our workforce and a talent pipeline to grow future leaders.

CORPORATE SOCIAL RESPONSIBILITY

In pursuit of our mission to deliver on the promise of mRNA science to create a new generation of transformative medicines for patients, we have scaled our operations, invested in research and building out our manufacturing and commercial capabilities, and hired top-tier talent. As we continue to mature, we believe it is important to develop long-term programs that underscore our commitment to corporate social responsibility. Please refer to the “Responsibility” section of our website, which can be found at www.modernatx.com, as well as our proxy statement related to our 2022 Annual Meeting of Stockholders that we will file with the SEC, for a description of some of the measures we have taken to support our commitment to corporate social responsibility.

COMPETITION

The biotechnology and pharmaceutical industries utilize rapidly advancing technologies and are characterized by intense competition. There is also a strong emphasis on defense of intellectual property and proprietary products.

mRNA Medicines and Our COVID-19 Vaccine

We believe that mRNA as a medicine coupled with our capabilities across mRNA technology, drug discovery, development, and manufacturing provide us with a competitive advantage. However, we face competition from others developing mRNA vaccines and therapeutics, as well as other medicines that compete or could compete with our mRNA products, development candidates and investigational medicines. We face competition from various sources, including large pharmaceutical companies, biotechnology companies, academic institutions, government agencies, and public and private research institutions. For any products that we eventually commercialize, we will not only compete with existing medicines but also compete with medicines that may become available in the future. We also face competition when entering into strategic alliances to advance and grow our pipeline.

We face significant competition in the market for our COVID-19 vaccine, particularly from established pharmaceutical companies with longer operating histories and significant experience in producing and marketing pharmaceutical products. In the United States, the U.S. FDA has granted a BLA to the Pfizer/BioNTech COVID-19 vaccine for the prevention of COVID-19 in individuals 16 years of age and older. The Pfizer/BioNTech COVID-19 vaccine has also been authorized under an EUA as a two-dose primary series for individuals five years of age and older, as a third primary series dose for individuals five years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster dose for individuals 12 years of age and older at least five months after completing a primary series of the vaccine. The Pfizer/BioNTech COVID-19 vaccine has also been authorized for use as a single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine. The CDC has recommended that individuals starting their COVID-19 vaccine series or receiving a booster dose receive either our COVID-19 vaccine or the Pfizer/BioNTech COVID-19 vaccine. The Johnson & Johnson/Janssen viral vector COVID-19 vaccine is also authorized under an EUA. Outside the United States, our COVID-19 vaccine has been authorized for use or approved in more than 70 countries, in addition to receiving authorization from the World Health Organization. In many of these jurisdictions, our vaccine is authorized for use in adolescents (ages 12-17). Internationally, our COVID-19 vaccine competes against over two dozen vaccines that have been authorized in various jurisdictions, and many other vaccine candidates remain in development, including other mRNA vaccines.

Additionally, competitors have developed treatments for COVID-19, and additional treatments may be developed in the future. For example, Pfizer and Merck have developed antiviral pills for the treatment of mild-to-moderate COVID-19 disease for certain adults who have tested positive for COVID-19. To the extent that these or other treatments are viewed as an alternative to vaccination against COVID-19, our competitive position could be harmed.

Competition for the sale of our COVID-19 vaccine can be impacted by a number of factors, including: the efficacy of our vaccine in preventing COVID-19 (particularly in the prevention of severe cases of COVID-19); the ability of our vaccine, or future iterations of the vaccine, and boosters to protect effectively against variants of the SARS-CoV-2 virus; perceptions of the efficacy of our vaccine; concerns about potential side effects from the vaccine, its safety or tolerability; the novelty of mRNA-based technology; storage and handling conditions for our vaccine and the ease or difficulty with which it can be distributed; the timing and scope of regulatory approvals; reimbursement coverage; our costs to produce and distribute our vaccine; and our ability to scale our manufacturing and distribution effectively as we continue to expand shipments internationally. The competitiveness of our COVID-19 vaccine in the future may also depend upon whether we are successful in efforts to combine the vaccine with other vaccines, like seasonal flu and RSV, and whether our competitors are successful in similar efforts. Additionally, standalone vaccines we may develop for respiratory diseases, such as seasonal flu vaccines, will face competition from existing vaccines and treatments, as well as future medicines developed by competitors. Our competitive positioning may also be affected by the fact that we do not have as long a history of producing pharmaceutical products or existing commercial relationships compared to certain of our competitors.

There are additional companies that are working on mRNA medicines, some of which have reached commercialization. Companies with mRNA programs include BioNTech and Pfizer (alone and in partnership with BioNTech and others). Other competitors include Sanofi (through the acquisition of Translate Bio), CureVac and GlaxoSmithKline, Arcturus Therapeutics, eTheRNA Immunotherapies Ethris, Genevant Sciences, Stemirna Therapeutics and Abogen Biosciences, which is developing a COVID-19 mRNA vaccine in collaboration with Walvax Biotechnology and the PLA Academy of Military Science. We also compete against other pharmaceutical companies in the market for COVID-19 vaccines that do not utilize mRNA-based technologies, including AstraZeneca and Johnson & Johnson, among others.

Beyond mRNA

We and our strategic collaborators face competition from companies developing therapies in various areas, other than the development of mRNA medicines, related to our collaborations. For example, there are a growing number of pharmaceutical, biotechnology and academic institutions researching and developing autologous and allogeneic CAR-T therapies in both the solid and liquid tumor setting. These CAR-T cell therapies are at various stages of development and approval and could compete against any CAR-T therapeutics we discover, develop and commercialize in collaboration with Carisma Therapeutics.

Similarly, there are many companies and institutions researching and developing CRISPR and other gene editing systems, which could compete against any therapies for genetic diseases we develop and commercialize in collaboration with Metagenomi or other collaborators.

GOVERNMENT REGULATION

Government authorities in the United States at the federal, state and local level and in other countries regulate, among other things, the research, development, manufacture and marketing of our products and product candidates. Generally, before a new drug or biologic can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained and submitted for review and approved by the regulatory authority.

U.S. drug and biological product development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations and biologics under the FDCA, the Public Health Service Act (PHSA), and their implementing regulations. Both drugs and biologics also are subject to other federal, state and local statutes and regulations. Failure to comply with applicable U.S. requirements at any time during the product development process, approval process or following approval may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, license revocation, a clinical hold, untitled or warning letters, voluntary or mandatory product recalls, market withdrawals, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement and civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Any of our investigational medicines must be approved by the FDA through a BLA or new drug application, NDA, process before they may be legally marketed in the United States. The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our current or future investigational medicines will be granted on a timely basis, or at all.

Preclinical studies

Before any of our product candidates may be tested in humans, the product candidate must undergo rigorous preclinical testing. Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess the potential for adverse events and in some cases to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations for safety/toxicology studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. An IND is a request for authorization from the FDA to administer an investigational product to humans and must become effective before human clinical trials may begin. Unless the FDA raises concerns, an IND automatically becomes effective 30 days after receipt by the FDA. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin.

Clinical trials

The clinical stage of development involves the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators and in accordance with GCP requirements. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an IRB for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to clinical trial subjects and monitors the clinical trial until completed. Further, progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA and more frequently in other situations, including the occurrence of serious adverse events. Information about certain clinical trials must be submitted within specific timeframes for publication on the www.clinicaltrials.gov website.

Under the U.S. National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (the NIH Guidelines), supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee (IBC), a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. While the NIH Guidelines are only mandatory for research being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Foreign studies conducted under an IND must meet the same requirements that apply to studies being conducted in the United States. Data from a foreign study not conducted under an IND may be submitted in support of a BLA if the study was conducted in accordance with GCP requirements, and the FDA is able to validate the data.

Clinical trials generally are conducted in three sequential phases, which may overlap:

- Phase 1 clinical trials generally involve a small number of healthy volunteers or disease-affected patients to assess the metabolism, pharmacologic action, side effect tolerability, and safety of the product candidate.
- Phase 2 clinical trials generally involve studies in disease-affected patients to evaluate proof of concept and/or determine the dosing regimen(s) for subsequent investigations. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, possible adverse effects and safety risks are identified, and a preliminary evaluation of efficacy is conducted.

- Phase 3 clinical trials generally involve a large number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product, and provide an adequate basis for product labeling.

The FDA may also require post-approval Phase 4 non-registrational studies to explore scientific questions to further characterize safety and efficacy during commercial use of a drug.

The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biologic has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the chemistry and physical characteristics of the drug or biologic as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and, among other things, companies must develop methods for testing the identity, strength, quality, and purity of the final product.

FDA review process

Following completion of the clinical trials, data are analyzed to assess whether the investigational product is safe and effective for the proposed indicated use or uses. The results of preclinical studies and clinical trials are then submitted to the FDA as part of a BLA or NDA, along with proposed labeling, chemistry, and manufacturing information to ensure product quality and other relevant data. A BLA is a request for approval to market a biologic for one or more specified indications and must contain proof of the biologic's safety, purity, and potency. An NDA for a new drug must contain proof of the drug's safety and efficacy. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of the FDA. FDA approval of a BLA or NDA must be obtained before a biologic or drug may be marketed in the United States.

Before approving a BLA or NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMP requirements and are adequate to assure consistent production of the product within required specifications. The FDA also may audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel products or products which present difficult questions of safety or efficacy to an advisory committee of expert advisors for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. The committee makes a recommendation to the FDA that is not binding but is generally followed.

After the FDA evaluates a BLA or NDA, it will grant marketing approval, request additional information or issue a complete response letter (CRL), outlining the deficiencies in the submission. The CRL may require additional testing or information, including additional preclinical or clinical data, for the FDA to reconsider the application. Even if such additional information and data are submitted, the FDA may decide that the BLA or NDA still does not meet the standards for approval. If the FDA grants approval, it issues an approval letter that authorizes commercial marketing of the product with specific prescribing information for specific indications.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product available in the United States for this type of disease or condition will be recovered from sales of the product.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years from the date of such approval, except in very limited circumstances, such if the latter product is shown to be clinically superior to the orphan product. Orphan drug exclusivity, however, also could block the approval of our products for seven years if a competitor first obtains approval of the same product as defined by the FDA or if our drug candidate is determined to be contained within the competitor's product for the same indication or disease.

Expedited development and review programs

The FDA may employ one of several tools to facilitate and expedite the development and review of a drug, including fast track designation, breakthrough therapy designation, accelerated approval and priority review designation. Fast track designation is designed to facilitate the development and review of a drug that treats a serious condition and fills an unmet medical need. Breakthrough therapy designation is designed to expedite the development and review of a drug that treats a serious condition and

preliminary clinical evidence demonstrates substantial improvement over available therapies. Priority review designation means the FDA's goal is to take action on an application within six months of filing. The FDA may grant priority review designation to a drug that would provide significant improvement in the safety or effectiveness of a treatment, diagnosis or prevention of a serious condition.

A product may also be eligible for accelerated approval if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies. In addition, it must demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug or biologic receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug or biologic shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the product. If the FDA determines that the conditions of approval are not being met, the FDA can withdraw its accelerated approval for such drug or biologic.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or the time period for FDA review or approval may not be shortened. Furthermore, fast track designation, priority review, accelerated approval, and breakthrough therapy designation do not change the standards for approval.

Emergency Use Authorization (EUA)

The Secretary of Health and Human Services (HHS) may authorize unapproved medical products to be marketed in the context of an actual or potential emergency that has been designated by the U.S. government. The COVID-19 pandemic has been designated as such an emergency. After an emergency has been announced, the Secretary of HHS may authorize the issuance of and the FDA Commissioner may issue EUAs for the use of specific products based on certain criteria, including that the product may be effective in diagnosing, treating, or preventing serious or life-threatening diseases when there are no adequate, approved, and available alternatives. From December 18, 2020, our COVID-19 vaccine was available under an EUA for active immunization to prevent COVID-19 in individuals 18 years of age and older. In January 2022, the FDA approved the BLA for our COVID-19 vaccine, Spikevax, to prevent COVID-19 in individuals 18 years of age and older in the United States. A booster dose of our COVID-19 vaccine at the 50 µg dose level is authorized for use under an EUA for adults 18 years and older. A third dose of our COVID-19 vaccine at the 100 µg dose level is authorized for use under an EUA in immunocompromised individuals 18 years of age or older in the United States who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. An EUA terminates when the emergency determination underlying the EUA terminates. An EUA is not a long-term alternative to obtaining FDA approval, licensure, or clearance for a product. The FDA may revoke an EUA for a variety of reasons, including if the underlying health emergency no longer exists or warrants such authorization.

In the United States, the Public Readiness and Emergency Preparedness Act, the PREP Act, provides immunity for manufacturers from all claims under state or federal law for "loss" arising out of the administration or use of a "covered countermeasure." However, injured persons may still bring a suit for "willful misconduct" against the manufacturer under some circumstances. "Covered countermeasures" include "qualified pandemic or epidemic products," including products intended to diagnose or treat pandemic or epidemic disease, such as pandemic vaccines. For these immunities to apply, the Secretary of HHS must issue a declaration in cases of public health emergency or "credible risk" of a future public health emergency. On March 17, 2020, the Secretary of HHS issued a declaration under the PREP Act and has issued subsequent amendments thereto since then to provide liability immunity for activities related to certain countermeasures against the ongoing COVID-19 pandemic. While we believe our products would be covered under the provisions of the PREP Act, this cannot be assured.

Pediatric information

Under the Pediatric Research Equity Act of 2003, all marketing applications for new active ingredients, indications, dosage forms, dosing regimens or routes of administration must contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred or inapplicable.

Under the Best Pharmaceuticals for Children Act, a product may be eligible for pediatric exclusivity, which adds six months to existing exclusivity periods and patent terms. This exclusivity may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued written request for such a study.

Post-approval requirements

Following approval of a new product, the manufacturer and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and record-keeping activities, reporting of adverse experiences, complying with promotion and advertising requirements, and limitations on industry-sponsored scientific and educational activities. Although physicians may prescribe legally available products for off-label uses, manufacturers may not market or promote such uses. Prescription drug and biologic promotional materials must be submitted to the FDA in conjunction with their first use. Further, if there are any modifications

to the drug or biologic, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new BLA or NDA or BLA or NDA supplement, which may require the development of additional data or preclinical studies and clinical trials.

The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy (REMS) to assure the benefits of the product outweigh the risks. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries, and other risk minimization tools. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures, including a REMS or the conduct of post-marketing studies to assess a newly discovered safety issue. Product approvals may be withdrawn for non-compliance with regulatory standards, or if problems occur following initial marketing.

FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP regulations. We and our third-party manufacturers must comply with cGMP regulations that require, among other things, quality control and quality assurance, the maintenance of records and documentation, and the obligation to investigate and correct any deviations from cGMP. Entities involved in the manufacture and distribution of approved drugs or biologics are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections for compliance with cGMP requirements and other laws. The discovery of violations could result in enforcement actions, and the discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA or NDA, including recall.

U.S. patent term restoration and marketing exclusivity

In certain circumstances, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch Waxman Amendments. The Hatch Waxman Amendments permit restoration of the patent term of up to five years as compensation for patent term lost during product development and FDA regulatory review process. Patent term restoration, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one half the time between the effective date of an IND and the submission date of a BLA or NDA, plus the time between the submission date of a BLA or NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for such an extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

If the FDA approves a drug product that contains an active ingredient not previously approved, the product is typically entitled to five years of non-patent regulatory exclusivity. Other products may be entitled to three years of exclusivity if approval was based on the FDA's reliance on new clinical studies essential to approval submitted by the NDA applicant. If the NDA applicant studies the product for use by children, the FDA may grant pediatric exclusivity, which extends by 180 days each existing exclusivity (patent and regulatory) related to the product.

An abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product was created by the Biologics Price Competition and Innovation Act of 2009 (the BPCI Act). Biosimilarity requires a showing that the product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the product and the reference product in terms of safety, purity, and potency. Interchangeability requires that a biological product be biosimilar to the reference product and that the product can be expected to produce the same clinical results as the reference product in any given patient and, for products administered multiple times to an individual, that the product and the reference product may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biological product. A reference biological product is granted 12 years of data exclusivity from the time of first licensure of the product and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product.

European Union drug development

Medicinal products can be marketed in the EU only if a marketing authorization from the competent regulatory agencies has been obtained. Similar to the United States, the various phases of preclinical and clinical research in the EU are subject to significant regulatory controls. Effective January 2022, the European Commission adopted a new Clinical Trials Regulation to streamline and harmonize the procedures for assessment and governance of clinical trials throughout the EU and to require that information on the authorization, conduct and results of each clinical trial conducted in the EU be publicly available.

Pediatric investigation plan

An application for marketing authorization of a medicinal product for human use that is not yet authorized in the EU must include a Pediatric Investigational Plan (PIP), unless a waiver applies. A scientific committee assesses the content of any PIP, waivers, and

deferrals for a medicinal product submitted to it in accordance with the regulation on medicinal products for pediatric use and formulates an opinion thereon.

European drug review and approval

In the European Economic Area (EEA), which is comprised of the 27 Member States of the EU and Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a marketing authorization. A company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology or those medicines intended to treat AIDS, cancer, neurodegenerative disorders, or diabetes, and optional for those medicines that are highly innovative, provides for the grant of a single marketing authorization that is valid for all EU Member States. In addition to the centralized procedure, the EEA also has a nationalized procedure, which requires a separate application to and approval determination by each country; a decentralized procedure, whereby applicants submit identical applications to several countries and receive simultaneous approval; and a mutual recognition procedure, where applicants submit an application to one country for review and other countries may accept or reject the initial decision.

European exclusivity

In the EEA, new innovative products authorized for marketing (i.e., reference products) qualify for eight years of data exclusivity and an additional two years of market exclusivity upon the grant of a marketing authorization. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. There is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity.

European orphan designation and exclusivity

Orphan drug designation is available in the EEA to promote the development of products that are intended for the diagnosis, prevention, or treatment of life threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU community, or where it is unlikely that the development of the medicine would generate sufficient return to justify the necessary investment in its development, and in each case for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or, if a method exists, the product would be a significant benefit to those affected). Medicinal products that receive and maintain orphan drug designation are entitled to 10 years of market exclusivity following approval.

European data collection

The Data Protection Directive and the General Data Protection Regulation (GDPR) governs the collection and use of personal data in the EU. The GDPR imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third-party processors in connection with the processing of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU, provides an enforcement authority and imposes large penalties for noncompliance, including the potential for fines of up to €20.0 million or 4.0% of the annual global revenues of the infringer, whichever is greater.

The UK has incorporated the GDPR (as it existed on December 31, 2020, but subject to certain UK specific amendments) into UK law (the UK GDPR). The UK GDPR and the UK Data Protection Act 2018 set out the UK's data protection regime, which is independent from but aligned to the EU's data protection regime. Although the UK is regarded as a third country under the EU's GDPR, the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing.

EU drug marketing

Like the Anti-Kickback Statute prohibition in the United States discussed below, the provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products is prohibited in the EU. Infringement of relevant EU laws could result in substantial fines and imprisonment. Payments may be made to physicians in limited circumstances, and in certain EU Member States such payments must be publicly disclosed. Moreover, agreements with physicians for the provision of services often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization, and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

Rest of the world regulation

Outside of the United States and the EU, the requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary from country to country. If we fail to comply with such requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions, or criminal prosecution.

Other healthcare laws

Healthcare providers, physicians, and third-party payors, including governmental payors such as Medicare and Medicaid will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Any arrangements with these parties may expose us to certain fraud and abuse and other healthcare laws and regulations. In the United States, these laws include, among others:

- The Anti-Kickback Statute, which makes it illegal for any person to knowingly and willfully solicit, receive, offer, or pay any remuneration, directly or indirectly, in cash or in kind, that is intended to induce or reward referrals, including the purchase, recommendation, order or prescription of a particular drug or any other good or service, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid.
- The federal False Claims Act, which imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities (including manufacturers) for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money to the federal government.
- Health Insurance Portability and Accountability Act of 1996 (HIPAA), which imposes criminal and civil liability for, among other things, knowingly and willfully executing a scheme, or attempting to execute a scheme, to defraud any healthcare benefit program, including private payors, or falsifying, concealing, or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH), and their respective implementing regulations, which impose, among other things, requirements on covered entities and their business associates relating to the privacy and security of individually identifiable health information.
- The Physician Payments Sunshine Act, enacted as part of the Patient Protection and Affordable Care Act, the ACA, which requires certain pharmaceutical manufacturers with products reimbursed under certain government programs to disclose annually to the federal government (for re-disclosure to the public) certain payments and other transfers of value provided to physicians, teaching hospitals and certain non-physician practitioners.
- Federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs.
- Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- Analogous state fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, which may be broader in scope and apply regardless of payor.

Additionally, certain state and foreign laws also govern the privacy and security of health information. Such data privacy and security laws may differ from each other in significant ways and often are not pre-empted by HIPAA, thus complicating compliance efforts. For example, the California Consumer Protection Act (CCPA) established a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. Further, the California Privacy Rights Act (CPRA), which is scheduled to take effect on January 1, 2023 (with certain provisions having retroactive effect to January 1, 2022), will create additional obligations with respect to processing and storing personal information. While clinical trial data and information governed by HIPAA are currently exempt from the current versions of the CCPA and CPRA, other personal information may be applicable and possible changes to the CCPA and CPRA may broaden its scope.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions, and settlements in the healthcare industry. If our operations are found to be in violation of any of these laws or other related governmental regulations, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, imprisonment, disgorgement, exclusion of drugs from government funded healthcare programs, such as Medicare and Medicaid, reputational harm, additional oversight, and reporting obligations if we become subject to a corporate integrity agreement or similar settlement to resolve allegations of non-compliance with these laws and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with

whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to similar actions, penalties, and sanctions. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business.

Current and future healthcare reform legislation

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our investigational medicines, restrict or regulate post-approval activities, and affect our ability to profitably sell any approved products. The ACA, for example, contains provisions that subject biological products to potential competition by lower-cost biosimilars and may reduce the profitability of drug products through increased rebates for drugs reimbursed by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and, annual fees based on pharmaceutical companies' share of sales to federal health care programs. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any strategic collaborators, may receive for any approved products.

In the United States, it is unclear whether the ACA will be overturned or further amended. We cannot predict what effect further changes to the ACA would have on our business. Additionally, other federal health reform measures have been proposed and adopted in the United States since the ACA was enacted, including the Budget Control Act of 2011, which includes provisions to reduce the federal deficit. The Budget Control Act, as amended, resulted in the imposition of 2% reductions in Medicare payments to providers, which began in April 2013 and will remain in effect through 2030 unless additional Congressional action is taken. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act (the CARES Act), as well as subsequent legislation, these reductions have been suspended from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. Then, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.

Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. In addition, the federal government, state legislatures, and foreign governments have shown significant interest in implementing cost containment programs, including price-controls, restrictions on reimbursement, and requirements for substitution of generic products for branded prescription drugs to limit the growth of government paid health care costs. For example, the federal government has passed legislation requiring pharmaceutical manufacturers to provide rebates and discounts to certain entities and governmental payors to participate in federal healthcare programs.

Environment

We are subject to state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act. These and other laws govern the use, handling and disposal of various biologic, chemical and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in foreign countries that impose similar obligations.

CORPORATE INFORMATION

We were incorporated under the laws of the State of Delaware on July 22, 2016. We are the successor in interest to Moderna LLC, a limited liability company formed under the laws of the State of Delaware in 2013. Moderna LLC was the successor in interest to Moderna Therapeutics, Inc., a Delaware corporation incorporated in 2009 as Newco LS18, Inc. by Flagship Pioneering. In August 2018, we changed our name from Moderna Therapeutics, Inc. to Moderna, Inc. Our principal corporate office is located at 200 Technology Square, Cambridge, MA 02139, and our telephone number is (617) 714-6500.

Our website, www.modernatx.com including the Investor Relations section, www.investors.modernatx.com; and corporate blog www.modernatx.com/moderna-blog; as well as our social media channels: Facebook, www.facebook.com/modernatx; Twitter, www.twitter.com/modernatx; and LinkedIn, www.linkedin.com/company/modernatx; contain a significant amount of information about us, including financial and other information for investors. We encourage investors to visit these websites and social media channels as information is frequently updated and new information is shared. The information on our website and that we disclose through social media channels is not incorporated by reference in this Annual Report on Form 10-K or in any other filings we make with the Securities and Exchange Commission (the SEC).

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Exchange Act. These include our Annual Reports on Form 10-K, our Quarterly Reports on Form 10-Q, and our

Current Reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding us and other issuers that file electronically with the SEC. The SEC's Internet website address is <http://www.sec.gov>.

Item 1A. Risk Factors

You should carefully consider the following risks and uncertainties, together with all other information in this Annual Report on Form 10-K. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations, and the market price of our common stock.

Risks related to COVID-19, mRNA-1273 and our other vaccine candidates against the SARS-CoV-2 virus

We may encounter difficulties producing, shipping or successfully commercializing our COVID-19 vaccine consistent with our existing or potential contractual obligations including due to delays or difficulties experienced by our commercial partners.

In response to the global COVID-19 pandemic, we are continuing to pursue the rapid manufacture, distribution and clinical testing of our COVID-19 vaccine (mRNA-1273), which is our only commercial product and source of product revenues. We may encounter difficulties producing the vaccine on the timelines and in the quantities set forth in our existing or future supply agreements. We may also be unsuccessful in entering into contracts for future sales of COVID-19 vaccines. Our ability to commercialize an effective vaccine depends on our manufacturing capability, both at our own manufacturing facility and those of our manufacturing partners, which we rapidly scaled in response to the pandemic. We are committing substantial financial resources and personnel to the development, manufacture and distribution of our COVID-19 vaccine, including to support the scale-up of manufacturing to enable our pandemic response, which may cause delays in or otherwise negatively impact our other development programs. We may need to, or the U.S. government may require us to, divert resources and capital from our other programs to the production of COVID-19 vaccines.

We do not have sufficient internal manufacturing infrastructure to support the global roll-out of our COVID-19 vaccine on our own. We have entered into strategic collaborations for the production, as well as for commercial fill-finish manufacturing, of our COVID-19 vaccine to supply markets both in and outside the United States. We may need to engage additional collaborators in the future, including contract manufacturing organizations (CMOs), government and non-government organizations, and other manufacturing partners, to assist in meeting our capacity needs. If we cannot enter into such arrangements on favorable terms, or at all, our ability to develop, manufacture and distribute our COVID-19 vaccine would be adversely affected.

Prior to 2020, we had not ramped up our organization for a commercial launch of any product, and doing so during a pandemic with an urgent, critical global need poses additional challenges, such as setting up distribution channels, building global teams with specialized skills, and managing potential intellectual property disputes or challenges. We may also face challenges sourcing a sufficient amount of raw materials to support the demand for our COVID-19 vaccine. We may be unable to effectively create a supply chain for the vaccine to adequately support demand as we rely on our third-party collaborators being able to fulfill demand. For example, we have in the past and may in the future experience international shipping delays as our supply chain expands and grows more complex. Any capacity or production issues or delays experienced by our collaborators may cause us to fail to meet certain product volume or delivery timing obligations under our COVID-19 supply agreements. Furthermore, we will require significant additional investment, whether from our own capital resources or other sources of funding, as we continue to expand our commercial launch efforts. We cannot guarantee that any of these challenges and requirements will be met in a timely manner or at all.

The pharmaceutical market is intensely competitive. We may be unsuccessful in competing effectively in the market for existing products, new treatment methods, and new technologies, including for COVID-19 vaccines.

The pharmaceutical market is intensely competitive and rapidly changing. Many pharmaceutical and biotechnology companies, academic institutions, governmental agencies, and public and private research organizations are pursuing the development of products for the same diseases that we are targeting or expect to target, including COVID-19 vaccines, and these institutions and competitors may have:

- greater financial, technical, manufacturing, and human resources than we have at every stage of the discovery, development, manufacture, and commercialization of products;
- more extensive experience in preclinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing, and selling products;
- multiple products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We face intense competition with respect to our COVID-19 vaccine from other vaccines and treatments, and our vaccine may not continue to compete favorably with existing or future products. Over two dozen COVID-19 vaccines have been authorized in various jurisdictions, including those produced by AstraZeneca, Johnson & Johnson, and Pfizer/BioNTech, and many more remain in development. These vaccines or other treatments, such as antiviral pills produced by Pfizer and Merck, may prove to be safer, more

effective, more convenient, have fewer side effects, be easier to ship or distribute, or able to be developed at a lower cost than our vaccine. These factors, or the perception of these factors, among others, could lead to a competitor's vaccine or other treatment to become the standard of care for COVID-19, have broader market acceptance, or be more successfully commercialized. The actual or perceived success or failure of other entities may adversely impact our ability to commercialize our COVID-19 vaccine.

We also will face competition from products that have already been approved and accepted by the medical community for the treatment of conditions we target. For example, we are developing a seasonal flu vaccine, for which there is a well-developed market, and we may be unsuccessful in developing a product or achieving market share. We also may compete with products that are under development for the treatment of conditions we target, which other products may be more effective, safer, less expensive, or marketed and sold more effectively.

If we successfully develop and obtain approval for investigational medicines, we will face competition based on many factors, including the safety and effectiveness of our products relative to any alternative therapies; the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration; the timing and scope of regulatory approvals; the availability and cost of manufacturing, marketing, and sales capabilities; the price of any approved medicine; reimbursement coverage; and patent position.

Our competitors may commercialize products with significant advantages over any products we develop, and may benefit from strategic alliances with or funding from larger pharmaceutical or biotechnology companies. If our competitors are more successful in commercializing their products than we are, our competitive position and business would be adversely affected. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our products, if approved.

We may be delayed or prevented from receiving full regulatory approval of our COVID-19 vaccine in certain jurisdictions or for certain demographics.

Efficacy, effectiveness, safety, and immunogenicity data with respect to our COVID-19 vaccine, as well as real-world evidence, continue to accumulate. Further results from clinical trials, as well as the experience of vaccinated individuals, could show diminished protection compared to the results released to date, as efficacy and antibody persistence wane over time. Additionally, we may observe new, more frequent or adverse events of greater severity in subjects participating in ongoing clinical trials or among those individuals vaccinated with our COVID-19 vaccine. For example, some studies have suggested that our vaccine may be associated with higher rates of myocarditis and pericarditis in young males compared to other COVID-19 vaccines. Unexpected safety issues could significantly damage our reputation and that of our mRNA platform, and lead to other issues, including delays in our other programs, the need to re-design our clinical trials and the need for significant additional financial resources. In addition, the interpretation of the data from our clinical trials of our COVID-19 vaccine by the FDA and other regulators may differ from our interpretation and such agencies may require us to conduct additional studies or analyses, which may lead to delays in obtaining authorization for these medicines. For example, in October 2021, the FDA requested that we explore a lower dosage for our COVID-19 vaccine in adolescents, which extended the length of clinical trials in this population, delaying potential authorization in the U.S. These factors could delay or prevent us from receiving regulatory approval of our COVID-19 vaccine in certain jurisdictions or for certain demographics.

The assays used to estimate the effectiveness of COVID-19 vaccines have only recently been developed and continue to evolve. Validation reports for these assays have been submitted for review to regulatory agencies. Results obtained in clinical studies of mRNA-1273 with later versions of these assays may be less positive than the results we have obtained to date. Moreover, blood samples from people who have recovered from COVID-19, used to benchmark the level of antibodies produced by subjects receiving mRNA-1273 in clinical studies, have been taken from a small number of people and may not be representative of the antibody levels in a broader population of people who have recovered from COVID-19, particularly as variant strains continue to emerge. The future results in clinical studies of mRNA-1273 may not be as positive when compared to the antibody levels in other blood samples.

We may be unsuccessful in developing future versions of our COVID-19 vaccine to protect against variants of the SARS-CoV-2 virus, or booster doses of our vaccine may not protect against such variants, and a market for vaccines and boosters against these variants may not develop.

Our original COVID-19 vaccine, mRNA-1273, was developed based upon the genetic sequence of the SARS-CoV-2 virus that was first detected in Wuhan, China. As the SARS-CoV-2 virus continues to evolve, new strains of the virus, or those that are already in circulation, may prove more transmissible or cause more severe forms of COVID-19 disease than the predominant strains to date. For example, the Omicron and Delta variants have been observed to be more transmissible, or contagious, than previous variants. There is a risk that mRNA-1273 will not be as effective in protecting against these or other future variant strains. For example, a standard two-dose inoculation of mRNA-1273 appears to be less effective at neutralizing the Omicron variant, which emerged in November 2021, than against the ancestral strain of SARS-CoV-2. Additionally, administration of booster doses of our vaccine may prove to be

ineffective, or less effective than desired, against certain variants. We have several development candidates against variants of concern, and may develop others in the future. If these efforts are unsuccessful, we are slower to develop variant-specific vaccines than competitors, or these vaccine candidates prove less effective than competitors' vaccines, these shortcomings may lead to reputational harm, loss of market share, and adverse financial results. It is also possible that we may expend significant resources adapting our COVID-19 vaccine or conducting clinical trials to protect against variants of the SARS-CoV-2 virus, but that a market for this adapted vaccine does not develop or demand does not align with our projections or cost expenditures.

The regulatory pathway for COVID-19 vaccines is continually evolving, and may result in unexpected or unforeseen challenges.

Our COVID-19 vaccine has moved rapidly through the regulatory review and authorization and approval processes in the U.S. and other jurisdictions. The speed at which COVID-19 vaccines and therapeutics are being created and tested is atypical, and evolving or changing plans or priorities within the FDA or other regulatory authorities, including changes based on new knowledge of COVID-19 and how the disease, and new variants of the virus, affect the human body, may significantly affect the regulatory timeline for further authorizations or approvals for our COVID-19 vaccine, including variant-specific versions of the vaccine. We cannot anticipate or predict with certainty the timelines or regulatory processes that may be required for the authorization or approval of updated versions of our COVID-19 vaccine, or vaccines that may be developed to fight against variants of the SARS-CoV-2 virus.

Although we currently operate under an EUA provided by the FDA for mRNA-1273 for as a booster dose for adults 18 years and older at least five months after completing a primary series of the vaccine, and as a third dose in immunocompromised individuals 18 years of age or older who have undergone solid organ transplantation, the FDA may revoke such authorization if it determines that the underlying health emergency no longer exists or warrants such authorization, and we cannot predict how long the EUA will remain in place. Such revocation could adversely impact our business in a variety of ways.

The EMA has made a positive recommendation for the administration of Spikevax for children ages 6 to 11, in addition to the existing conditional marketing authorization from the EMA for Spikevax in adults and adolescents ages 12 and older. Although a conditional marketing authorization is a formal marketing authorization and covers all batches produced for the EU, we are obliged to provide certain additional information and data by specified timelines as conditions of the authorization, and the EMA can take regulatory action if we fail to comply. Conditional marketing authorizations are valid for one year and can be renewed annually; however, the EMA may decide not to renew. If new data emerges that shows the benefits of our vaccine do not continue to outweigh its risks, the EMA can suspend or revoke our authorization. Similar temporary, emergency authorizations that we have received for mRNA-1273 could be revoked if the conditions for granting the authorization no longer apply. Any such revocation of the temporary authorization to distribute mRNA-1273, without receiving final approval to distribute the vaccine, could adversely impact our ability to realize the full financial benefit of our existing or future supply agreements.

Our ability to deliver our vaccine to customers may be curtailed by one or more government actions or interventions, which may be more likely during a global health crisis, such as the COVID-19 pandemic.

It is possible that one or more government entities may take actions that directly or indirectly diminish our rights or opportunities with respect to our COVID-19 vaccine, limiting our economic prospects. In the United States, the Defense Production Act of 1950, as amended (the Defense Production Act), gives the U.S. government rights and authorities that may directly or indirectly diminish such rights or economic opportunities. Our current and potential third-party service providers may be impacted by government entities potentially invoking the Defense Production Act or other potential restrictions to all or a portion of services they might otherwise offer.

Government entities imposing restrictions or limitations on our third-party service providers may require us to obtain alternative service sources for our COVID-19 vaccine or our vaccine candidates. If we are unable to timely enter into alternative arrangements on satisfactory terms, we will experience delays in the development or production of our COVID-19 vaccine and our vaccine candidates, increased expenses, and delays in distribution or commercialization of our COVID-19 vaccine, or, when and if approved, our vaccine candidates.

In addition, our supply contracts with the U.S. government for our COVID-19 vaccine restrict our ability to export vaccine that is produced from our U.S.-dedicated supply chain to markets outside the United States prior to satisfying our delivery obligations to the U.S. government. Furthermore, governments have threatened to block or limit the export of COVID-19 vaccines manufactured in their territories in instances where manufacturers have been delayed or have not fully satisfied their delivery obligations to those governments. Governments of the jurisdictions in which we or our contract manufacturing partners produce our COVID-19 vaccine may impose export restrictions, prohibiting us from delivering our COVID-19 vaccine to customers in other jurisdictions. The imposition of export controls could severely and adversely impact our manufacturing activities, commercial activities and financial results.

In addition, during a global health crisis, such as the COVID-19 pandemic, where the spread of a disease needs to be controlled, closed or heavily regulated, national borders create challenges and potential delays in our development and production activities and may necessitate that we pursue strategies to develop and produce our vaccines and vaccine candidates within self-contained national or international borders, at potentially much greater expense and with longer timeframes for public distribution.

Risks related to our pipeline, product development and regulatory review

Preclinical development is lengthy and uncertain, especially for a new class of medicines such as mRNA, and therefore our preclinical programs or development candidates may be delayed, terminated, or may never advance to the clinic, any of which may have a material adverse impact on our platform or our business.

Much of our pipeline is in preclinical development, and these programs could be delayed or not advance into the clinic. Before we can initiate clinical trials for a development candidate, we must complete extensive preclinical studies, including IND-enabling good laboratory practice (GLP) toxicology testing, to support our planned INDs in the United States, or similar applications in other jurisdictions. We must also complete extensive work on Chemistry, Manufacturing, and Controls (CMC) activities (including yield, purity and stability data) to be included in an IND submission. CMC activities for a new class of medicines such as mRNA require extensive manufacturing processes and analytical development, which is uncertain and lengthy. For instance, batch failures as we scale up our manufacturing have occurred and may continue to occur. In addition, we have in the past and may in the future have difficulty identifying appropriate buffers and storage conditions to enable sufficient shelf life of batches of our development candidates. If we must produce new batches, preclinical studies or clinical trials could be delayed. We cannot be certain of the timely completion or outcome of our preclinical testing and studies, whether the FDA or other regulators will accept the results, or if the outcome of our preclinical testing, studies, and CMC activities will ultimately support the further development of our programs. As a result, we cannot be sure that we will be able to submit INDs or similar applications for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulators allowing clinical trials to begin.

Clinical development is lengthy and uncertain, especially with a new class of medicines such as mRNA medicines. Clinical trials of our investigational medicines may be delayed and certain programs may never advance in the clinic or may be more costly to conduct than we anticipate, any of which could have a material adverse impact on our platform or our business.

Clinical testing is expensive, complex and lengthy, and its outcome is inherently uncertain. There is a high rate of attrition for product candidates proceeding through clinical trials and most investigational medicines that commence clinical trials are never approved as products. We may not be able to initiate, may experience delays in, or may have to discontinue clinical trials for our investigational medicines. We and our strategic collaborators also may experience unforeseen events during, or as a result of, any clinical trials that we or they conduct that could delay or prevent us or them from successfully developing our investigational medicines and gaining approval from regulators. Delays or other events that might prevent us from proceeding with clinical trials include:

- regulators, Institutional Review Boards (IRBs), or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on favorable terms with prospective trial sites and prospective contract research organizations (CROs);
- changes to the scale and site of our manufacturing could lead to significant delays or changes in our clinical trial designs;
- the outcome of our preclinical studies and our early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results;
- we may be unable to establish or achieve clinically meaningful endpoints for our studies;
- if we make changes to our investigational medicines after clinical trials have commenced (which we have done in the past), we may be required to repeat earlier stages or delay later stages of clinical testing;
- clinical trials of any investigational medicines may fail to show safety or efficacy, or produce negative or inconclusive results, and we may decide, or regulators may require us to conduct additional nonclinical studies or clinical trials, or we may decide to abandon product development programs;
- preclinical and clinical data are often susceptible to varying interpretations and analyses, and many investigational medicines believed to have performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval;
- our investigational medicines, or other medicines in the same class as ours, may have undesirable side effects, such as the immunogenicity of the LNPs or their components, the immunogenicity of the protein made by the mRNA, or degradation products, any of which could lead to serious adverse events, or other effects;
- administration of our LNPs could lead to systemic side effects related to the components of the LNPs and could contribute, in whole or in part, to one or more of the following: immune reactions, infusion reactions, complement reactions, opsonization reactions, antibody reactions, or reactions to PEG;

- significant adverse events or other side effects could be observed in our trials, including those involving dosing of young, human subjects with an investigational medicine;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or withdraw from the trial, which may require that we add new clinical trial sites;
- regulators may impose a complete or partial clinical hold on a trial, or we or our investigators, IRBs, or ethics committees may elect to suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to an unacceptable benefit-risk ratio;
- regulators may impose a complete or partial clinical hold on clinical trials of other companies working on mRNA medicines;
- the cost of preclinical or nonclinical testing and studies and clinical trials of any investigational medicines may be greater than we anticipate;
- the supply or quality of our investigational medicines or other materials necessary to conduct clinical trials may be insufficient or inadequate;
- safety and efficacy concerns regarding one or more of our investigational medicines will be considered by us and by the FDA and other global regulators as we pursue clinical trials of new investigational medicines, develop effective informed consent documentation and work with IRBs and scientific review committees (SRCs);
- safety or efficacy concerns could arise from nonclinical or clinical testing of other therapies targeting a similar disease state or other therapies, such as gene therapy, that are perceived as similar to ours;
- adverse side effects could be observed in future clinical trials where our investigational medicines are administered in combination with other therapies (such as the co-administration of our PCV investigational medicine, mRNA-4157); and
- a lack of adequate funding to continue a particular clinical trial.

The FDA has indicated that, prior to commencing later-stage clinical trials for our programs, we will need to develop assays to measure and predict the potency of a given dose of our investigational medicines. Any delay in developing assays that are acceptable to the FDA or other regulators could delay the start of future clinical trials. Additionally, we have conducted and may conduct in the future clinical trials that utilize an “open-label” trial design, where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an approved drug or placebo. The results from an open-label trial may not be predictive of future clinical trial results from a controlled environment with a placebo or active control. Further, the FDA or other regulators may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials. Significant preclinical or nonclinical testing and studies or clinical trial delays for our investigational medicines could allow our competitors to bring products to market before we do. Any delays in the development of our investigational medicines may harm our business, financial condition, and prospects significantly.

There are risks that are unique to each of our programs and modalities and risks that are applicable across programs and modalities. These risks may impair our ability to advance one or more of our programs in clinical development, obtain regulatory approval, or ultimately commercialize our products, or cause us to experience significant delays in doing so, any of which may materially harm our business.

We have a large pipeline of development candidates and investigational medicines, of which many are in clinical trials or have an open IND. Certain features in our development candidates and investigational medicines, including those related to mRNA, chemical modifications, surface chemistries, LNPs, and their components, may result in risks that apply to some or all of our programs and modalities. As our development candidates and investigational medicines progress, we or others may determine that: certain of our risk allocation decisions were incorrect or insufficient; we made platform-level technology mistakes; individual programs or our mRNA science in general has technology or biology risks that were unknown or under-appreciated; our choices on how to develop our infrastructure to support our scale will result in an inability to manufacture our investigational medicines for clinical trials or otherwise impair our manufacturing; or we have allocated resources in such a way that we cannot recover large investments or rapidly re-direct capital.

We utilize earlier programs in a modality to understand the technology risks within the modality, including manufacturing and pharmaceutical properties. Even if our earlier programs in a modality are successful in any phase of development, any program may fail at a later phase of development, and other programs within the same modality may fail at any phase of development, including at phases where earlier programs in that modality were successful. This may be a result of technical challenges unique to that program or due to biology risk, which is unique to every program. The biology risk across the majority of our pipeline represents targets and pathways not clinically validated by one or more approved drugs, and the risk that the targets or pathways that we have selected may not be effective will continue to apply across the majority of our current and future programs.

As we progress our programs through clinical development, new technical challenges may arise that cause an entire modality to fail. Additionally, any portfolio spanning risks, whether known or unknown, if realized in any one of our programs, would have a material and adverse effect on our other programs and on our business as a whole.

There are also specific additional risks to certain of our modalities and our programs as a whole. For example, prophylactic vaccines typically require clinical testing in up to tens of thousands of healthy volunteers to define an approvable benefit-risk profile. The need to show a high degree of safety and tolerability when dosing healthy individuals could result in rare and even spurious safety findings, negatively impacting a program prior to or after commercial launch. Even if we observe positive safety, tolerability, and levels of immunogenicity in early clinical trials, there can be no assurance that we will observe acceptable safety or efficacy profiles in later-stage trials required for approval of these programs.

For neoantigen cancer vaccines, to date, no molecular (non-cell-based) therapeutic protein vaccine has been shown to be effective against cancer and there are many clinical and manufacturing challenges to personalized medicines, including cell-based therapies and vaccines. These risks include: a rapid production turn-around time that is measured in weeks in order to supply patients in our clinical trials before further progression and mutation of their tumors, the significant costs incurred in making individualized vaccines, and potential lack of immune responses due to the biology of the tumor or immune status of the patient. These risks apply to our personalized cancer vaccine (PCV) and other neoepitope investigational medicine programs. Additionally, there may be challenges in delivering an adequate quantity of active pharmaceutical ingredient (API) required to drive efficacy due to the limitation in volume of API that can be delivered to a specific location, like a tumor or injured tissue. Our investigational therapies for local injections often require specialized skills for conducting a clinical trial that could delay trials or slow or impair commercialization of an approved investigational medicine due to the poor adoption of injected local therapeutics or intratumoral therapies. In addition, the uncertain translatability of target selection from preclinical animal models, including mouse and non-human primate models, to successful clinical trial results may be impossible, particularly for immuno-oncology and systemic therapies, and cancer vaccines. In general, several biological steps are required for delivery of mRNA to translate into therapeutically active medicines. These processing steps may differ between individuals or tissues, potentially leading to variable levels of therapeutic protein, variable activity, immunogenicity, or variable distribution to tissues for a therapeutic effect. Gene therapies and mRNA-based medicines may activate one or more immune responses against any and all components of the drug product (e.g., the mRNA or the delivery vehicle, such as an LNP) as well as against the encoded protein, giving rise to potential immune reaction related adverse events. Eliciting an immune response against the encoded protein may impede our ability to achieve a pharmacologic effect upon repeat administration or a side effect. These risks apply to all of our programs, including our systemic secreted therapeutics and systemic intracellular therapeutics modalities.

We may experience delays in identifying and enrolling participants in our clinical trials, which would delay the progress of our investigational medicines and result in increased expenses.

Identifying and qualifying trial participants for our clinical trials of our investigational medicines is critical to our success. Difficulties or delays in enrollment may result in increased costs or may affect the timing or outcome of our planned clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of our investigational medicines and obtain regulatory approval of potential products.

We may be unable to identify, recruit, and enroll a sufficient number of trial participants, or those with required or desired characteristics to achieve diversity in a trial, to complete our clinical trials in a timely manner. As we did in our Phase 3 clinical study of mRNA-1273, we may slow enrollment in a trial to focus on achieving greater diversity in the subject population. Patient and subject enrollment is affected by factors including:

- severity of the disease under investigation;
- complexity and design of the study protocol;
- size of the patient population;
- eligibility criteria for the study in question, including age-based eligibility criteria limiting subject enrollment to adolescent or pediatric populations;
- proximity and availability of clinical study sites for prospective trial participants;
- availability of competing therapies and clinical trials, including by third parties or our own clinical trials;
- patient referral practices of physicians;
- ability to monitor trial participants adequately during and after treatment;
- ability to recruit clinical trial investigators with the appropriate competencies and experience;
- clinicians' and trial participants' perceptions as to the potential advantages and side effects of the investigational medicine being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating;
- adverse results or other adverse safety signals in our trials or related to other investigational medicines, and the resulting negative publicity, which could discourage potential trial participants and their doctors from participating in our trials;
- in the case of our PCV, the need to wait for the manufacture of the personalized drug product; and
- our ability to obtain and maintain participant informed consent.

We also have entered into strategic alliances under which our strategic collaborators control the development of certain of our investigational medicines, which may provide us limited or no ability to influence the enrollment rate of our clinical trials. Even if we or our strategic collaborators are able to enroll trial participants, there is no guarantee that they will ultimately be dosed as part of, or complete, a clinical trial.

mRNA drug development has substantial clinical development and regulatory risks due to the novel nature of this new class of medicines, and the negative perception of the efficacy, safety, or tolerability profile of any investigational medicines that we or others develop could adversely affect our ability to conduct our business, advance our investigational medicines, or obtain regulatory approvals.

No mRNA medicine has been granted full or conditional approval by the FDA or other regulators, other than COVID-19 vaccines. Successful discovery and development of mRNA medicines by us or our strategic collaborators is highly uncertain and depends on numerous factors, many of which are beyond our or their control. We constantly make business decisions and take calculated risks to advance our development efforts and pipeline, including those related to mRNA technology, delivery technology, and manufacturing processes, which ultimately may be unsuccessful.

Our mRNA investigational medicines that appear promising in the early phases of development may fail to advance, experience delays in the clinic, experience clinical holds, or fail to reach the market for many reasons, including:

- nonclinical or preclinical study, or clinical trial, results may show potential mRNA medicines to be less effective than desired or to have harmful or problematic side effects or toxicities;
- adverse results in our clinical trials, or in those of others developing similar products, or adverse effects relating to mRNA, or our LNPs, may lead to negative publicity or delays in or termination of one or more of our programs;
- adverse events related to products that are perceived to be similar to mRNA medicines, such as those related to gene therapy or gene editing, could result in a decrease in the perceived benefit of one or more of our programs, increased regulatory scrutiny, decreased confidence by patients and clinical trial collaborators in our investigational medicines, and less demand for any product that we may develop;
- the insufficient ability of our translational models to reduce risk or predict outcomes in humans, particularly given that each component of our investigational medicines and development candidates may have a dependent or independent effect on safety, tolerability, and efficacy, which may, among other things, be species-dependent;
- manufacturing failures or insufficient supply of cGMP materials for clinical trials, or higher than expected cost could delay or set back clinical trials, or make mRNA-based medicines commercially unattractive;
- changes that we make to optimize our manufacturing, testing or formulating of cGMP materials could impact the safety, tolerability, and efficacy profile of our investigational medicines and development candidates;
- pricing or reimbursement issues or other factors that delay clinical trials or make any mRNA medicine uneconomical or noncompetitive with other therapies;
- our large pipeline of development candidates and investigational medicines could result in a greater quantity of reportable adverse events, including suspected unexpected serious adverse reactions, other reportable negative clinical outcomes, manufacturing reportable events or material clinical events that could lead to clinical delay or hold by the FDA or applicable regulatory authority or other clinical delays, any of which could negatively impact the perception of one or more of our programs, as well as our business as a whole;
- failure to timely advance our programs or a failure or delay in receiving necessary regulatory approvals due to, among other factors, slow or failure to complete enrollment in clinical trials, withdrawal by trial participants from trials, failure to achieve trial endpoints, additional time requirements for data analysis, data integrity issues, preparation of a BLA, or the equivalent application, discussions with the FDA or EMA, a regulatory request for additional nonclinical or clinical data, or safety formulation or manufacturing issues may lead to our inability to obtain sufficient funding;
- new legislation or regulations passed by U.S., state, or foreign governments in response to negative public perception of mRNA medicines; and
- the proprietary rights of others and their competing products and technologies that may prevent our mRNA medicines from being commercialized.

Because we are developing some of our development candidates or investigational medicines for the treatment of diseases in which there is little clinical experience and, in some cases, using new endpoints or methodologies, the FDA or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results.

There are no pharmacologic therapies approved to treat the underlying causes of many diseases that we currently attempt to address or may address in the future. For instance, for both MMA and PA, few clinical trials have been attempted, and there are no approved drugs to treat these diseases. As a result, the design and conduct of clinical trials of investigational medicines for the treatment of these disorders and other disorders may take longer, be more costly, or be less effective due to the novelty of development in these diseases.

Even if the FDA does find our success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoint to a degree of statistical significance in any pivotal or other clinical trials we or our strategic collaborators conduct. Further, even if we do achieve the pre-specified criteria, our trials may produce results that are unpredictable or inconsistent with the results of the more traditional efficacy endpoints in the trial. The FDA could give overriding weight to other efficacy endpoints over a primary endpoint, even if we achieve statistically significant results on that endpoint, if we do not do so on our secondary efficacy endpoints. The FDA also weighs the benefits of a product against its risks and may view the efficacy results in the context of safety as not being supportive of licensure. Regulators in other countries may make similar findings with respect to these endpoints.

Some of our investigational medicines are classified as gene therapies by the FDA and the EMA. The association of our medicines with gene therapies could result in increased regulatory burdens, impair the reputation of our investigational medicines, or negatively impact our platform or our business.

There have been few approved gene therapy products in the United States or foreign jurisdictions, and there have been well-reported significant adverse events associated with their testing and use. Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future, and the implications for mRNA-based therapies are unknown. For example, the FDA has established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research (CBER) to consolidate the review of gene therapy and related products, and convenes the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. In the EU, mRNA has been characterized as a gene therapy medicinal product, which falls within a broader category known as Advanced Therapy Medicinal Products (ATMPs), which are subject to additional regulatory requirements. In certain countries, mRNA therapies have not yet been classified or any such classification is not known to us; for example, in Japan, the Pharmaceuticals and Medical Devices Agency has not taken a position on the regulatory classification. Notwithstanding the differences between mRNA medicines and gene therapies, the classification of some of our mRNA investigational medicines as gene therapies in the United States, the EU, and potentially other countries could adversely impact our ability to develop our investigational medicines, negatively impacting our platform and our business. For instance, a clinical hold on gene therapy products may apply to our mRNA investigational medicines irrespective of the differences between gene therapies and mRNA.

Adverse events reported with respect to gene therapies could adversely impact one or more of our programs. Although our mRNA development candidates and investigational medicines are generally designed not to make any permanent changes to cell DNA, regulatory agencies or others could believe that adverse effects of gene therapies caused by introducing new DNA and irreversibly changing the DNA in a cell could also be a risk for our mRNA investigational therapies, and as a result may delay one or more of our trials or impose additional testing for long-term side effects. Any new requirements and guidelines promulgated by regulatory review agencies may negatively affect our business by lengthening the regulatory review process, requiring us to perform additional or larger studies, or increasing our development costs, any of which could lead to changes in regulatory positions and interpretations, delay or prevent advancement or approval and commercialization of our investigational medicines, or lead to significant post-approval studies, limitations, or restrictions. As we advance our investigational medicines, we will be required to consult with these regulatory agencies and advisory committees and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of some or all of our investigational medicines.

Additionally, we have established Moderna Genomics (MGX) with the vision of becoming a leader in large, complex genomic editing. In November 2021, we announced a multi-year research collaboration with Metagenomi to leverage Metagenomi's discovery platform and expertise to develop next-generation *in vivo* gene editing therapies. Our work in genomic editing is subject to all risks associated with gene therapies. Although there have been significant advances in recent years in fields of gene therapy and genome editing, *in vivo* CRISPR-based genome editing technologies are relatively new and their therapeutic utility is largely unproven. Public perception and related media coverage of potential therapy-related efficacy or safety issues, as well as ethical concerns related specifically to genome editing, may adversely influence the willingness of subjects to participate in clinical trials. In addition, any review conducted by an institutional biosafety committee may result in delay or prevent initiation of a gene therapy clinical trial.

Additionally, if any such therapeutic is approved, physicians and patients may be slow or fail to accept these novel and personalized treatments. Physicians, health care providers and third-party payors often are slow to adopt new products, technologies and treatment practices, particularly those that may also require additional upfront costs and training. Physicians may not be willing to undergo training to adopt these novel and potentially personalized therapies, may decide the particular therapy is too complex or potentially risky to adopt without appropriate training, and may choose not to administer the therapy. Further, due to health conditions, genetic profile or other reasons, certain patients may not be candidates for the therapies. In addition, responses by federal and state agencies, congressional committees and foreign governments to negative public perception, ethical concerns or financial considerations may result in new legislation, regulations, or medical standards that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. Based on these and other factors, health care providers and payors may decide that the benefits of these new therapies do not or will not outweigh their costs.

A breakthrough therapy designation or fast track designation, or accelerated approval, by the FDA or comparable pathways in other jurisdictions for a drug may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that the drug will receive marketing approval.

We have received Fast Track Designation for some of our investigational medicines and may seek Fast Track Designation or breakthrough therapy designation for others. The FDA has broad discretion whether or not to grant either designation, and the receipt of either designation for a drug may not result in a faster development process, review, or approval compared to drugs considered for approval under conventional FDA procedures. Even if one or more of our investigational medicines qualify for Fast Track Designation or as breakthrough therapies, the FDA may later decide that the investigational medicine no longer meets the conditions for qualification or it may decide that the time period for FDA review or approval will not be shortened. Additionally, even if we obtain accelerated approval in the United States or under comparable pathways in other jurisdictions, we may face requirements and limitations that will adversely affect our prospects. For example, the FDA generally requires pre-approval of promotional materials for products receiving accelerated approval, which could adversely impact the timing of the commercial launch of the product. Further, we may not receive ultimate approval or we may be approved only for a limited indication, we may not successfully complete required post-approval trials, such trials may not confirm the clinical benefit of our drug, or approval of the drug may be withdrawn.

We may fail to obtain and maintain orphan drug designations for our investigational medicines.

We may file for orphan drug designation where available for our investigational medicines. We may never receive such designation for any particular medicine. Although we have received orphan drug designation from both the FDA and the European Commission for PA (mRNA-3927) and GSD1a (mRNA-3745), orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication, or may be lost if the FDA later determines that the request for designation was materially defective. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may be approved for the same condition, and only the first applicant to receive approval will receive the benefits of marketing exclusivity. Even after an orphan-designated product is approved, the FDA can subsequently approve a later drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior if it is shown to be safer, more effective, or makes a major contribution to patient care.

Our investigational medicines may face competition from biosimilars approved through an abbreviated regulatory pathway.

During the 12-year period of exclusivity provided by the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, another company may still market a competing version of a product if the FDA approves a BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials demonstrate the safety, purity, and potency of the other company's product. The BPCI Act is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty.

There is also a risk that any exclusivity we receive for an investigational medicine could be shortened due to Congressional action or otherwise, or that the FDA will not consider our investigational medicines to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCI Act, some of which may impact the BPCI Act's exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

If we cannot obtain, or are delayed in obtaining, required regulatory approvals, we will be unable to commercialize, or will be delayed in commercializing, investigational medicines we may develop.

Any mRNA medicine we may develop and the activities associated with its development and commercialization, including design, testing, manufacture, record-keeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and comparable foreign regulators. To obtain required regulatory approvals to commercialize any of our investigational medicines, we and our strategic collaborators must demonstrate through extensive preclinical studies and clinical trials that our products are safe, pure, and potent in humans, including the target population. Successful completion of clinical trials is a prerequisite to submitting a BLA to the FDA, a marketing authorization application (MAA) to the EMA, and similar marketing applications to comparable global regulatory authorities, for each investigational medicine and, consequently, the ultimate approval and commercial marketing of any investigational medicines.

We have not received approval to market any investigational medicine, other than our COVID-19 vaccine, in any jurisdiction, and our current or future development candidates or investigational medicines may never obtain regulatory approval. We have limited experience in filing and supporting the necessary applications for marketing approvals and may need to rely on third-party CROs or

regulatory consultants to assist us in this process. Although we expect to submit BLAs for our mRNA-based investigational medicines in the United States, other jurisdictions may consider our mRNA-based investigational medicines to be new drugs, not biologics, and require different marketing applications. Preclinical studies and clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and approval in one country does not guarantee regulatory approval in another. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any investigational medicines we develop may be ineffective, only moderately effective, or have undesirable or unintended side effects, toxicities, or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

Additionally, the process of obtaining marketing approvals, both in the United States and abroad, is expensive, time-consuming, and uncertain, and can vary substantially based upon a variety of factors, including the type, complexity, and novelty of the investigational medicines involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may delay the review of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical, or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of an investigational medicine. Additional delays or non-approval may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval.

The FDA and other regulators review the CMC section of regulatory filings. Any aspects found unsatisfactory by regulatory agencies may result in delays in clinical trials and commercialization. In addition, the regulatory agencies conduct pre-approval inspections at the time of a BLA. Any findings by regulatory agencies and failure to comply with requirements may lead to delay in approval and failure to commercialize the potential investigational medicine.

If we experience delays in obtaining approval or if we fail to obtain approval of any investigational medicines we may develop, the commercial prospects for those investigational medicines will be harmed, and our ability to generate revenues will be materially impaired.

Our products are, and any future products will be, subject to regulatory scrutiny.

Even if we obtain regulatory approval in a jurisdiction, the applicable regulatory authority may still impose significant restrictions on the indicated uses or marketing of our product, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling, or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our investigational medicines.

If we, our contract manufacturers or other strategic collaborators fail to comply with applicable regulatory requirements following approval of any of our investigational medicines, a regulatory agency may: issue a warning letter asserting that we are in violation of the law; seek an injunction or impose civil or criminal penalties or monetary fines; suspend or withdraw regulatory approval or revoke a license; suspend any ongoing clinical trials; refuse to approve a pending BLA or supplements to a BLA submitted by us; seize or recall investigational medicines or products; or refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any approved products and generate revenues.

Additionally, the FDA or other regulators could require us to adopt a Risk Evaluation and Mitigation Strategy for any approved investigational medicine to ensure that the benefits of treatment outweigh the risks for each potential patient, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, extensive patient monitoring, or distribution systems and processes that are highly controlled, restrictive, and more costly than what is typical for the industry. Furthermore, if we or others later identify undesirable side effects caused by any product that we develop, several potentially significant negative consequences could result, including the suspension or withdrawal of approvals and licenses; the addition of warning labels; changes to the way a product is administered; the requirement to conduct further clinical trials; lawsuits or increased liability for harm to patients and their children; and reputational harm. Any of these events could prevent us from achieving or maintaining market acceptance of any products we develop and could have a material adverse impact on our business, financial condition, results of operations, and prospects.

Even though the Moderna COVID-19 Vaccine/Spikevax has been approved by the FDA for individuals 18 years of age and older in the United States, it remains the subject of regulatory scrutiny. For example, we are required to conduct post-marketing studies to further assess the risks of myocarditis and pericarditis following vaccination with Spikevax. Additionally, we have committed to conducting additional post-marketing safety studies, including conducting a pregnancy registry study to evaluate pregnancy and infant outcomes after receipt of Spikevax during pregnancy. We or others could identify previously unknown side effects, or known side effects could be observed as being more frequent or severe than in clinical studies or earlier post-marketing periods, in which case:

- sales of mRNA-1273 may be more modest than originally anticipated;
- the FDA and other regulatory agencies may revoke authorizations for the vaccine;
- we may decide, or be required, to conduct recalls or send field alerts to physicians, pharmacists and hospitals;
- additional nonclinical or clinical studies, changes in labeling, or changes to manufacturing processes, specifications and/or facilities may be required; and
- government investigations or lawsuits, including class-action lawsuits, may be brought against us.

Any of the above occurrences could reduce or prevent sales of our COVID-19 vaccine, increase our expenses and impair our ability to successfully commercialize the vaccine.

Risks related to the manufacturing of our commercial products, development candidates, investigational medicines and our future pipeline

Our mRNA products, including our COVID-19 vaccine, development candidates and investigational medicines are based on novel technologies and are complex and difficult to manufacture. We or our third-party manufacturers may encounter difficulties in manufacturing, product release, shelf life, testing, storage, supply chain management, or shipping for any of our medicines.

The manufacturing processes for our medicines, including our COVID-19 vaccine, are novel and complex. No mRNA medicine, other than COVID-19 vaccines, has been commercialized to date. Due to the novel nature of mRNA technology and our limited experience at larger scale production, we and our collaborators have experienced and may continue to encounter difficulties in manufacturing, product release, shelf life, testing, storage, supply chain management, or shipping. These issues could be due to many reasons, including complexities of producing batches at larger scale, equipment failure, human error, choice and quality of raw materials and excipients, analytical testing technology, and product instability. Further, mRNA medicines encapsulated in LNPs must be developed and manufactured under well-controlled conditions, or pharmacological activity can be adversely impacted.

In an effort to optimize product features, we have in the past and may in the future make changes to our development candidates or investigational medicines in their manufacturing and stability formulation and conditions. This has in the past and may in the future result in our having to resupply batches for preclinical or clinical activities when there is insufficient product stability during storage and insufficient supply. Insufficient stability or shelf life of our development candidates and investigational medicines could materially delay our or our strategic collaborators' ability to continue the clinical trial for that development candidate or investigational medicine or require us to begin a new clinical trial with a newly formulated drug product, due to the need to manufacture additional preclinical or clinical supply.

Our rate of innovation is high, which has resulted in and will continue to cause a high degree of technology change that can negatively impact product comparability during and after clinical development. Furthermore, technology changes may drive the need for changes in, modification to, or the sourcing of new manufacturing infrastructure or may adversely affect third-party relationships.

In many cases, we may need to utilize multiple batches of drug substance and drug product to meet the clinical supply requirement of a single clinical trial. Failure in our ability to scale up batch size or failure in any batch may lead to a substantial delay in our clinical trials or in the commercialization of any approved product. For example, the changes we make as we continue developing new manufacturing processes for our drug substance and drug product may impact specification and stability of the drug product, and may lead to failure of batches, resulting in a substantial delay in delivery of commercial product or conduct of our clinical trials. Our mRNA investigational medicines may prove to have a stability profile that leads to a lower than desired shelf life of the final approved mRNA medicine. This poses risk in supply requirements, wasted stock, and higher cost of goods.

We are dependent on a number of equipment providers who are also implementing novel technology. Further, we have developed our own custom manufacturing equipment for certain of our medicines. If we encounter unexpected performance issues with such equipment, we could encounter delays or interruptions to clinical and commercial supply. Due to the number of different programs, we may have cross contamination of investigational medicines inside of our factories, CROs, suppliers, or in the clinic that affect the integrity of our investigational medicines.

As we scale the manufacturing output for commercial production and particular programs, we plan to continuously improve yield, purity, and the pharmaceutical properties of our commercial products, development candidates and investigational medicines from

IND-enabling studies through commercial launch, including shelf life stability, and solubility properties of drug product and drug substance. Because of continuous improvement in manufacturing processes, we may switch processes for a particular program during development. However, after a change in process, more time will be required for pharmaceutical property testing, such as 6 or 12 month stability testing. That may require resupplying clinical material or making additional cGMP batches to keep up with clinical trial demand before such pharmaceutical property testing is completed.

We are utilizing a number of raw materials and excipients that have a single source of supply, are new to the pharmaceutical industry, and are being employed in a novel manner. Some of these raw materials and excipients have not been scaled to a level to support commercial supply and could experience unexpected manufacturing or testing failures, or supply shortages. Such issues with raw materials and excipients could cause delays or interruptions to clinical and commercial supply of our investigational medicines.

We have established a number of analytical assays, and may have to establish several more, to assess the quality of our mRNA investigational medicines. We may identify gaps in our analytical testing strategy that might prevent release of product or could require product withdrawal or recall. For example, we may discover new impurities that have an impact on product safety, efficacy, or stability. This may lead to an inability to release mRNA investigational medicines until the manufacturing or testing process is rectified.

As our drug development pipeline increases and matures, the increased demand for clinical and commercial supplies from our facilities and third parties may impact our ability to operate. We rely on many service providers, all of whom have inherent risks in their operations that may adversely impact our operations.

Completion of our clinical trials and commercialization of our vaccine candidates require access to, or development of, facilities to manufacture our vaccine candidates at sufficient yields and at commercial-scale. We have limited experience manufacturing any of our vaccine candidates in the volumes that are necessary to support large-scale clinical trials or commercial sales. Efforts to establish these capabilities may not meet initial expectations as to scheduling, scale-up, reproducibility, yield, purity, cost, potency or quality. If we are unable to institute necessary controls related to product development, manufacturing and quality, our operations may be adversely impacted. In addition, other companies, many with substantial resources, compete with us for access to the materials needed to manufacture our vaccines.

We currently utilize, and expect to continue to utilize, third parties to, among other things, manufacture raw materials, components, parts, and consumables, and to perform quality testing. If the field of mRNA and other nucleic acid medicines continues to expand, we may encounter increasing competition for these materials and services. Demand for third-party manufacturing or testing facilities may grow at a faster rate than their existing capacity, which could disrupt our ability to find and retain third-party manufacturers capable of producing sufficient quantities of such raw materials, components, parts, and consumables required to manufacture our mRNA investigational medicines. The use of service providers and suppliers could expose us to risks, including, but not limited to:

- termination or non-renewal of supply and service agreements with third parties in a manner or at a time that is costly or damaging to us;
- disruptions to the operations of these suppliers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the supplier or service provider; and
- inspections of third-party facilities by regulatory authorities that could have a negative outcome and result in delays to or termination of their ability to supply our requirements.

Our reliance on third-party manufacturers may adversely affect our operations or result in unforeseen delays or other problems beyond our control. Because of contractual restraints and the limited number of third-party manufacturers with the expertise, required regulatory approvals and facilities to manufacture our bulk vaccines on a commercial scale, replacement of a manufacturer may be expensive and time-consuming and may cause interruptions in the production of our vaccine. A third-party manufacturer may also encounter difficulties in production, including:

- difficulties with production costs, scale up and yields;
- availability of raw materials and supplies;
- quality control and assurance;
- shortages of qualified personnel;
- compliance with strictly enforced regulations that vary in each country where products might be sold; and
- lack of capital funding.

Any delay or interruption could adversely affect our business, financial condition, or results of operations.

We are subject to operational risks associated with the physical and digital infrastructure at both our internal manufacturing facilities and at those of our external service providers.

Our MTC facility in Norwood, Massachusetts incorporates a significant level of automation of equipment with integration of several digital systems to improve efficiency of operations. Our high level of digitalization may pose risk of process equipment malfunction and even overall manufacturing system failure or shutdown due to internal or external factors including, but not limited to, design issues, system compatibility, or potential cybersecurity breaches.

Our facilities or those of our contract manufacturers may also be subject to intentional attacks or acts of sabotage by outside actors, contractors or employees. Any disruption in our or our contract manufacturers' manufacturing capabilities could cause delays in production capacity for our drug substances or products or a shutdown of facilities, could impose additional costs, or may require us to identify, qualify, and establish an alternative manufacturing site, the occurrence of which could adversely affect our business, financial condition, results of operations, and prospects.

As we expand our development and commercial capacities, we have and expect that we will continue to establish additional manufacturing capabilities inside the MTC footprint and that we will expand to other locations and geographies, such as Africa, Australia and Canada. This expansion may lead to regulatory delays or prove more costly than anticipated. If we fail to select a suitable location, complete construction in an efficient manner, engage effectively with local regulators, recruit the required personnel, and generally manage our growth effectively, the development and production of commercial products or our investigational medicines could be delayed or curtailed. We expect that we will continue to make additional investments in our manufacturing processes as we expand the MTC and our other manufacturing infrastructure.

Our products and investigational medicines are sensitive to shipping and storage conditions, which, in some cases, requires cold-chain logistics and subjects our investigational medicines to risk of loss or damage.

Our COVID-19 vaccine and our investigational medicines are sensitive to temperature, storage, and handling conditions, and we could lose medicines if the product or product intermediates are not stored or handled properly. Shelf life for our products and investigational medicines is expected to be variable, and our investigational medicines may expire prior to use. Cold-chain logistics are required for certain of our investigational medicines and our COVID-19 vaccine. If we or third-party distributors do not maintain effective cold-chain supply logistics, then we may experience an unusual number of returned or out of date products and critical batches of products may be rendered unusable. This has in the past and could in the future lead to additional manufacturing costs and delays in our ability to supply required quantities for clinical trials, commercial sale, or otherwise. In addition, the cost associated with such transportation services and the limited pool of vendors could cause supply disruptions.

We are subject to significant regulatory oversight with respect to manufacturing our COVID-19 vaccine and our mRNA investigational medicines. Our manufacturing facilities or the manufacturing facilities of our third-party manufacturers or suppliers may not meet regulatory requirements. Failure to meet cGMP requirements set forth in regulations promulgated by the FDA, EMA, and other global health authorities could result in significant delays in any approval of and costs of our products.

The manufacturing of medicines for clinical trials or commercial sale is subject to extensive regulation, and components of such products must be manufactured in accordance with cGMP requirements, which are enforced, in the case of the FDA, in part through its facilities inspection program. The regulations govern manufacturing processes and procedures, including record keeping, and the implementation and operation of quality systems to control and assure the quality of products and materials used in clinical trials. Poor control of the cGMP production processes can lead to product quality failures that can impact our ability to supply product, resulting in cost overruns and delays to clinical timelines, which could be extensive. Such production process issues include but are not limited to:

- critical deviations in the manufacturing process;
- facility and equipment failures;
- contamination of the product due to an ineffective quality control strategy;
- facility contamination as assessed by the facility and utility environmental monitoring program;
- raw material failures due to ineffective supplier qualification or regulatory compliance issues at critical suppliers;
- ineffective product stability;
- ineffective corrective actions or preventative actions taken to correct or avoid critical deviations due to our developing understanding of the manufacturing process as we scale; and
- failed or defective components or consumables.

Regulatory authorities typically require representative manufacturing site inspections to assess adequate compliance with cGMP and manufacturing controls. If we or one of our third-party manufacturing sites fails to provide sufficient quality assurance or control, the product approval to commercialize may not be granted. Inspections by regulatory authorities may occur at any time during the

development or commercialization phase of products. The inspections may be product specific or facility specific for broader cGMP inspections, or as a follow up to market or development issues that the regulatory agency may identify. Deficient inspection outcomes may negatively impact the ability of our third-party manufacturers or suppliers to fulfill their supply obligations, impacting or delaying supply or delaying programs.

The manufacturing process for our COVID-19 vaccine, and for any other products that we may develop, is subject to the FDA and foreign regulatory authority approval process. If we or our third-party manufacturers are unable to reliably produce products or investigational medicines to specifications acceptable to the FDA or other regulatory authorities, we or our strategic collaborators may not obtain or maintain the approvals needed to commercialize such products. Even if regulatory approval is obtained for any of our mRNA medicines, there is no assurance that either we or our CMOs will be able to manufacture the approved medicine to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our investigational medicines, impair commercialization efforts, or increase our cost of goods, which, in turn, could have an adverse effect on our business, financial condition, results of operations, and prospects.

In addition, we may not have direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance, and qualified personnel. Our contract manufacturers supply or manufacture materials or products for other companies, and their failure to meet applicable regulatory requirements may generally affect the regulatory status of their facilities. In addition, to the extent that we rely on foreign contract manufacturers, including for our COVID-19 vaccine, we are subject to additional risks, including the need to comply with import and export regulations. Additionally, our potential future dependence on others to manufacture our investigational medicines and raw materials may adversely affect our future profit margins and our ability to commercialize any products that receive regulatory approval on a timely and competitive basis.

The FDA, the EMA, and other foreign regulatory authorities may require us to submit product samples of any lot of any approved product, together with the protocols showing the results of applicable tests, at any time. In some cases, regulators may prohibit us from distributing a lot or lots until it authorizes release. Deviations in the manufacturing process, including those affecting quality attributes and stability, may cause unacceptable changes in the product, resulting in lot failures or product recalls. Our third-party contract manufacturers have experienced lot failures and one has experienced a product recall related to our COVID-19 vaccine. Lot failures have in the past caused, and lot failures or product recalls in the future with respect to product produced by either our own or our third-party manufacturers' facilities could cause, us and our strategic collaborators to delay clinical trials or product launches, which could harm our business, financial condition, results of operations, and prospects.

We and our manufacturing partners also may encounter problems hiring and retaining the experienced scientific, quality control, and manufacturing personnel needed to operate our manufacturing processes and operations or those of our manufacturing partners, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements. Additionally, we may not be able to control for or ultimately detect intentional sabotage or negligence by any employee or contractor.

Our PCV investigational medicine is uniquely manufactured for each patient using a novel, complex manufacturing process and we may encounter difficulties in production.

We custom design and manufacture PCVs that are unique and tailored specifically for each patient. Manufacturing unique lots of PCVs is susceptible to product loss or failure due to issues with:

- logistics associated with the collection of a patient's tumor, blood, or other tissue sample;
- shipping such samples to a facility for genetic sequencing;
- next generation sequencing of the tumor mRNA;
- identification of appropriate tumor-specific mutations;
- the use of a software program, including proprietary and open source components, which is hosted in the cloud and a part of our investigational medicine, to assist with the design of the patient-specific mRNA, which software must be maintained and secured;
- effective design of the patient-specific mRNA that encodes for the required neoantigens;
- batch specific manufacturing failures or issues that arise due to the uniqueness of each patient-specific batch;
- quality control testing failures;
- unexpected failures of batches placed on stability;
- shortages or quality control issues with single-use assemblies, consumables, or critical parts sourced from third-party vendors that must be changed out for each patient-specific batch;
- significant costs associated with individualized manufacturing that may adversely affect our ability to continue development;
- successful and timely manufacture and release of the patient-specific batch;
- shipment issues encountered during transport of the batch to the patient site of care; and

- the ability to define a consistent safety profile at a given dose when each participant receives a unique vaccine.

We have built and installed custom manufacturing equipment for PCVs that has been incorporated into a personalized vaccine unit in the MTC. This equipment may not function as designed, resulting in deviations in the drug product produced, which could lead to increased batch failure and the inability to supply patients enrolled in the clinical trial. If our clinical development plans are expanded, due to the custom nature of the equipment and single-use assemblies, we may require significant investments. In addition, it would take considerable time to scale up our facilities or build new facilities to meet any commercial demand if our PCV product is approved. This expansion or addition of new facilities could also lead to product comparability issues, which could further delay introduction of new capacity.

Because our PCVs are manufactured for each individual patient, we are required to maintain a chain of identity with respect to each patient's tissue sample, sequence data derived from such tissue sample, results of analysis of such patient's genomic analysis, and the custom manufactured product for each patient. Maintaining such a chain of identity is difficult and complex, and failure to do so has in the past and may in the future result in product mix up, adverse patient outcomes, loss of product, or regulatory action including withdrawal of any approved products from the market. Further, as our PCV is developed through early-stage clinical trials to later-stage clinical trials towards approval and commercialization, we expect that multiple aspects of the complicated collection, analysis, manufacture, and delivery process will be modified in an effort to optimize processes and results. These changes may not achieve the intended objectives, and any of these changes could cause our PCVs to perform differently than we expect, potentially affecting the results of clinical trials.

Risks related to our reliance on third parties

We are dependent on single-source suppliers for some of the components and materials used in, and the processes required to develop, our products, development candidates and investigational medicines.

We depend on single-source suppliers for some of the components and materials used in, and manufacturing processes required to develop and commercialize, our COVID-19 vaccine, development candidates and investigational medicines. We cannot ensure that these suppliers will remain in business, have sufficient capacity or supply to meet our needs, or that they will not be purchased by one of our competitors or another company that will cease working with us. Our use of single-source suppliers exposes us to several risks, including disruptions in supply, price increases, or late deliveries. Any disruption in supply from any single-source supplier could lead to supply delays or interruptions that would damage our business, financial condition, results of operations, and prospects.

There are, in general, relatively few alternative sources of supply for substitute components. If we have to switch to a replacement supplier, the manufacture and delivery of our products, development candidates or investigational medicines could be interrupted for an extended period, which could adversely affect our business. Establishing additional or replacement suppliers for any of the components or processes used in our products or investigational medicines, if required, may not be accomplished quickly, if at all. Any replacement supplier would need to be qualified and may require additional regulatory authority approval, resulting in further delay. Any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand for our investigational medicines. Additionally, as part of the FDA's approval of our investigational medicines, the FDA will review the individual components of our process, which include the manufacturing processes and facilities of our single-source suppliers.

We have in the past entered into, and in the future may enter into, strategic alliances with third parties for the development and commercialization of our and their products, development candidates and investigational medicines. If these strategic alliances are not successful, our business could be adversely affected.

We have entered into strategic alliances under which our strategic collaborators have provided, and may in the future provide, funding and other resources for developing, manufacturing and commercializing our investigational medicines. Additionally, as we have begun to generate revenue, we have begun to enter into strategic alliances where we agree to provide funding and other resources to third parties. We expect to enter into additional strategic alliances in the future. Our existing strategic alliances, and any future strategic alliances we enter into, may pose a number of risks, including the following:

- strategic collaborators may not perform their obligations as expected;
- the clinical trials conducted as part of such strategic alliance may not be successful;
- strategic collaborators may not pursue development and commercialization of any investigational medicines that achieve regulatory approval or may elect not to continue or renew development or commercialization of programs based on clinical trial results, changes in the strategic collaborators' focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

- strategic collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial, abandon an investigational medicine, repeat or conduct new clinical trials, or require a new formulation of an investigational medicine for clinical testing;
- strategic collaborators could develop, independently or with third parties, products that compete directly or indirectly with our products or investigational medicines if such collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- products or investigational medicines developed in strategic alliances with us may be viewed by our strategic collaborators as competitive with their own investigational medicines or products, which may cause strategic collaborators to cease to devote resources to the development or commercialization of our investigational medicines;
- a strategic collaborator with marketing and distribution rights to one or more of our products or investigational medicines that achieve regulatory approval may commit insufficient resources to the marketing and distribution of any such product;
- disagreements with strategic collaborators, including over proprietary rights, contract interpretation, or the course of development of any investigational medicines, may cause delays or termination of the research, development, or commercialization of such investigational medicines, lead to additional responsibilities for us with respect to such investigational medicines, or result in litigation or arbitration, any of which would be time-consuming and expensive;
- strategic collaborators may not properly maintain or defend our IP rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our IP or proprietary information;
- disputes may arise with respect to the ownership of IP developed pursuant to our strategic alliances;
- strategic collaborators may infringe the IP rights of third parties, exposing us to potential litigation and liability;
- future relationships may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business;
- we could face significant competition in seeking appropriate strategic collaborators and the negotiation process is time-consuming and complex; and
- our international operations through any future collaborations, acquisitions, or joint ventures may expose us to certain operating, legal, and other risks not encountered in the United States.

Our strategic collaborators generally may materially amend or terminate their agreements with us for convenience, which has happened in the past. If any collaboration agreement is terminated, we may not receive future research funding or milestone, earn-out royalty or other contingent payments, and the development of our investigational medicines may be delayed. It may also be difficult to attract new strategic collaborators to continue development or commercialization of the applicable investigational medicine, and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval, and commercialization described in this Annual Report on Form 10-K apply to the activities of our strategic collaborators.

We may seek to establish additional strategic alliances and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans. Certain of our strategic alliance agreements may restrict our ability to develop certain products.

Our development programs and the potential commercialization of our development candidates and investigational medicines will require substantial additional cash to fund expenses. We may collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of some of our investigational medicines, and we face significant competition in seeking appropriate strategic collaborators. Our ability to establish additional strategic alliances will depend, among other things, on our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed strategic alliance, and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject investigational medicine, the costs and complexities of manufacturing and delivering such investigational medicine to trial participants, the potential of competing drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. Any potential strategic collaborator may ultimately collaborate on alternative investigational medicines or technologies for similar indications rather than collaborate with us.

We are also restricted under our existing strategic alliance agreements from entering into agreements on certain terms with potential strategic collaborators to pursue other targets on our own. These restrictions on working with targets, polypeptides, routes of administration, and fields could limit our ability to enter into strategic collaborations with other collaborators or to pursue certain potentially valuable development candidates or investigational medicines.

Strategic alliances are complex and time-consuming to negotiate and document. If we cannot negotiate and enter into new strategic alliances on a timely basis, on favorable terms, or at all, we may need to curtail the development of the investigational medicine for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and

undertake development or commercialization activities at our own expense. We may need to obtain additional capital to fund these efforts, and the inability to obtain such funding on favorable terms may prevent us from further developing our investigational medicines or bringing them to market and generating product revenue.

We rely on and expect to continue to rely on third parties to conduct aspects of our research, preclinical studies, protocol development, and clinical trials for our development candidates and investigational medicines. If these third parties do not perform satisfactorily, comply with regulatory requirements, or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our investigational medicines and our business could be substantially harmed.

We rely on third parties such as CROs to help manage certain preclinical work and our clinical trials, and on medical institutions, clinical investigators and CROs to assist in the design and review of, and to conduct, our clinical trials, including enrolling qualified patients. In addition, we engage third-party contractors and collaborators to support numerous other research, commercial and administrative activities, which reduces our control over these activities but does not relieve us of our responsibilities, such as ensuring that each of our clinical trials is conducted in accordance with its general investigational plan and protocols. Moreover, the FDA requires us to comply with GLPs and good clinical practices for conducting, recording and reporting the results of preclinical studies and clinical trials to assure that data and reported results are credible and accurate and that in the case of clinical trials the rights, integrity and confidentiality of trial participants are protected. Such standards will evolve and subject us and third parties to new or changing requirements.

If third parties do not successfully carry out their contractual duties or meet expected deadlines, we may need to replace them, which could cause a delay of the affected clinical trial, drug development program or applicable activity. If clinical trials are not conducted in accordance with our contractual expectations or regulatory requirements, action by regulatory authorities may significantly and adversely affect the conduct or progress of such trials or even require a clinical trial to be redone. Accordingly, our efforts to obtain regulatory approvals for and commercialize our drug candidates could be delayed. In addition, failure of any third-party contractor to conduct activities in accordance with our expectations could adversely affect the relevant research, development, commercial or administrative activity.

Risks related to our intellectual property

If we are not able to obtain and enforce patent protection for our discoveries, or protect the confidentiality of our trade secrets, our ability to effectively compete using our development candidates will be harmed.

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop under the patent and other IP laws of the United States and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. Because certain U.S. patent applications are confidential until the patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date which will not be filed in foreign countries, third parties may have filed patent applications for technology covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions, including our COVID-19 vaccine. For this and other reasons, we may be unable to secure desired patent rights, thereby losing exclusivity. Further, we may be required to obtain licenses under third-party patents to market our proposed products or conduct our research and development or other activities. If licenses are not available to us on favorable terms, we may not be able to market the affected products or conduct the desired activities.

The process of obtaining patent protection is expensive and time-consuming and our pending patent applications may not result in issued patents. Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by governmental patent agencies, and our patent applications may fail to result in valid enforceable patents, or our patent protection could be reduced or eliminated, for non-compliance with these requirements. If we or our present or future strategic collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business may be adversely affected.

Despite our and our strategic collaborators' efforts to protect our proprietary rights, unauthorized parties may obtain and use information that we regard as proprietary. While issued patents are presumed valid, they may not survive a validity challenge and could be held unenforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable, or circumvented by parties seeking to design around our IP. Also, third parties or the USPTO may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation, or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management, could reduce or eliminate royalty payments to us from third-party licensors, and could have a material adverse impact on our business.

The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts, and lawmakers. For example, the America Invents Act, which took effect in March 2013, included a number of changes to the patent laws of the United States. If any of the enacted changes prevent us from adequately protecting our discoveries, including our ability to pursue infringers of our patents to obtain injunctive relief or for substantial damages, our business could be adversely affected. One major provision of the America Invents Act changed U.S. patent practice from a first-to-invent to a first-to-file system. If we fail to file an invention before a competitor files on the same invention, we no longer have the ability to provide proof that we were in possession of the invention prior to the competitor's filing date, and thus would not be able to obtain patent protection for our invention. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents. In certain countries, for example, methods for the medical treatment of humans are not patentable.

Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. We also rely to a certain extent on trade secrets, know-how, and technology, which are not protected by patents, to maintain our competitive position. We also rely on non-disclosure agreements and invention assignment agreements entered into with our employees, consultants, and third parties. If any trade secret, know-how, or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected.

Failure to obtain and maintain all available regulatory exclusivities and broad patent scope and to maximize patent term restoration or extension on patents covering our products may lead to loss of exclusivity and early biosimilar entry resulting in a loss of market share and/or revenue.

In addition, we may choose not to enforce our IP rights in certain circumstances or for certain periods of time. For example, in October 2020 we announced that while the COVID-19 pandemic continues, we will not enforce our COVID-19-related patents against those making vaccines intended to combat the pandemic. We also noted that to eliminate any perceived IP barriers to vaccine development during the pandemic period, upon request we are also willing to license our IP for COVID-19 vaccines to others for the post-pandemic period. However, we may never enter into such licenses of our IP for the post-pandemic period, and our business may be otherwise adversely impacted by our decision not to enforce this IP.

Uncertainty over IP in the pharmaceutical and biotechnology industry has been the source of litigation and other disputes, which is inherently costly and unpredictable, and can have adverse financial and freedom-to-operate consequences.

mRNA medicines are a relatively new scientific field and, as the field continues to mature, patent applications are being processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as patent infringement lawsuits, interference, reexamination, and opposition proceedings, as well as inter-partes and post-grant-review proceedings introduced by provisions of the America Invents Act, in various patent offices relating to patent rights in the mRNA field.

We have issued patents and pending patent applications in the United States and in key markets around the world that claim many different methods, compositions, and processes relating to the discovery, development, manufacture, and commercialization of mRNA medicines and our delivery technology, including LNPs. An opposition has been filed against one of our European platform patents covering uridine-modified mRNAs and we expect that further oppositions will be filed in the European Patent Office (EPO) and elsewhere relating to patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims. We cannot be certain that such patent will survive or that the claims will remain in the current form. Even if our rights are not directly challenged, disputes could lead to the weakening of our IP rights.

There are many issued and pending third-party patents that claim aspects of oligonucleotide and delivery technologies that we may need for our mRNA therapeutic and vaccine candidates or marketed products, including our COVID-19 vaccine. There are also many issued third-party patents that claim targeting genes or portions of genes that may be relevant for mRNA medicines we wish to develop. For example, there are issued and pending patent applications that may be asserted against us in a court proceeding or otherwise based upon the asserting party's belief that we may need such patents for our mRNA therapeutic candidates. Thus, it is possible that one or more organizations hold patent rights to which we may need a license or which could be asserted against us. If those organizations refuse to license such patent rights on reasonable terms or a court rules that we need such patent rights that have

been asserted against us and we are not able to obtain a license on reasonable terms, we may owe damages to such party, and further may be unable to market products, including our COVID-19 vaccine, covered by such patents.

In certain instances, we have instituted and may in the future institute inter partes review proceedings against issued U.S. patents and opposition proceedings against European patents owned by third parties in the field of mRNA medicines. We have a number of these proceedings ongoing against third-party patents related to RNA vaccinations and mRNA delivery. If we are unsuccessful in invalidating such third-party patents, those third parties may attempt to assert those patents against investigational medicines that obtain regulatory approval, including our COVID-19 vaccine. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our development candidates may be subject to claims of infringement of the patent rights of third parties.

If we become involved in patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, substantial liability for damages, or be required to stop our product development and commercialization efforts.

There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture, or methods for treatment related to the use or manufacture of our investigational medicines, and third parties may assert that we are employing their proprietary technology without authorization. In addition, third parties may obtain patents in the future and claim that our technologies infringe upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our investigational medicines, any molecules formed during the manufacturing process, or any final product itself, the holders of any such patents may obtain injunctive or other equitable relief, which could effectively block our ability to commercialize such investigational medicine unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture, or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable investigational medicine unless we obtained a license or until such patent expires.

Defense of infringement and other claims, regardless of their merit, would involve substantial litigation expense and divert employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products, or obtain one or more licenses from third parties, which may not be made available on commercially favorable terms, if at all, or may require substantial time and expense.

In addition, any such licenses are likely to be non-exclusive and, therefore, our competitors may have access to the same technology licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability, which could jeopardize our ability to sustain our operations. Moreover, we expect that a number of our collaborations will provide that royalties payable to us for licenses to our IP may be offset by amounts paid by our collaborators to third parties who have competing or superior IP positions in the relevant fields, which could result in significant reductions in our revenues from products developed through collaborations.

In addition, in connection with certain license and strategic alliance agreements, we have agreed to indemnify certain third parties for certain costs incurred in connection with litigation relating to IP rights or the subject matter of the agreements. The cost to us of any litigation or other proceeding relating to IP rights, even if resolved in our favor, could be substantial, and litigation would divert our management's efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could delay our research, development and commercialization efforts and limit our ability to continue our operations.

If third-party owners of any patent rights that we license do not properly or successfully obtain, maintain, or enforce the patents underlying such licenses, our competitive position and business prospects may be harmed.

We may become a party to licenses that give us rights to third-party IP that is necessary or useful for our business. In such a case, our success may depend in part on the ability of our licensors to obtain, maintain, and enforce patent protection for our licensed IP. Our licensors may not successfully prosecute the patent applications we license. Even if patents issue in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the IP we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. In addition, we sublicense our rights under various third-party licenses to our strategic collaborators. Any impairment of these sublicensed rights could result in reduced revenues under our strategic alliance agreements or result in termination of an agreement by one or more of our strategic collaborators.

If we fail to comply with our obligations in the agreements under which we license IP rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We license IP, which involves complex legal, business, and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. We are a party to certain IP license agreements and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license and may be subject to additional liabilities.

In certain cases, we control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our strategic collaborators. Disputes may arise regarding IP subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether our technology and processes that are not subject to the licensing agreement infringe on IP of the licensor;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of IP by our licensors and us and our strategic collaborators; and
- the priority of invention of patented technology.

If disputes over IP that we have licensed prevent or impair our ability to maintain our current licensing arrangements on favorable terms, we may be unable to successfully develop and commercialize the affected development candidates or investigational medicines. We are generally also subject to all of the same risks with respect to protection of IP that we license as we are for IP that we own. If we or our licensors fail to adequately protect this IP, our ability to commercialize products could suffer.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. From time to time, we are subject to claims that we or our employees, consultants, or independent contractors, have inadvertently or otherwise used or disclosed IP, including trade secrets or other proprietary information, of third parties, including our employees' former employers. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable IP rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims challenging the inventorship or ownership of our patents and other IP.

We may be and have been subject to claims that former employees, collaborators, or other third parties have an ownership interest in our patents or other IP. Ownership disputes may arise, for example, from conflicting obligations of consultants or others who are involved in developing our development candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable IP rights, including exclusive ownership of, or right to use, valuable IP. Such an outcome could have a material adverse impact on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and distract management and other employees, and could impact or patenting strategy.

Changes in U.S. patent and regulatory law could impair our ability to protect our products.

Our success is heavily dependent on IP, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and the process is costly, time-consuming and inherently uncertain. In addition, the United States has enacted and is implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. These rulings have increased uncertainty with regard to our ability to obtain patents in the future, as well as with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. See "—Risks related to the research, development, regulatory review, and

approval of our existing and future pipeline—Our investigational medicines may face competition from biosimilars approved through an abbreviated regulatory pathway.”

We may not be able to protect our IP rights throughout the world.

Filing, prosecuting, and defending patents on development candidates and investigational medicines in every country would be prohibitively expensive, and our foreign IP rights can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect IP rights to the same extent as U.S. federal and state laws. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies to develop their own products in jurisdictions where we have not obtained patent protection or may export infringing products to territories where we have patent protection, but enforcement is not as strong as in the United States. These products may compete with our products.

Many companies have encountered significant problems in protecting and defending IP rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other IP protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our IP rights around the world may be inadequate to obtain a significant commercial advantage from the IP that we develop or license.

Additionally, many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. As a result, in response to the COVID-19 pandemic, it is possible that certain countries may take steps to facilitate compulsory licenses that permit the distribution of a COVID-19 vaccine in those countries. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the relevant patent rights. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected.

Our reliance on government funding and collaboration from governmental and quasi-governmental entities for certain of our programs adds uncertainty to our research and development efforts with respect to those programs and may impose requirements that increase the costs of development, commercialization and production of any programs developed under those government-funded programs.

The development of our Zika vaccine (mRNA-1893) is funded by BARDA and our COVID-19 vaccine was developed in collaboration with NIAID. BARDA has agreed to fund the advancement of our COVID-19 vaccine to FDA licensure. Contracts and grants funded by the U.S. government and its agencies, including our agreements funded by BARDA and DARPA and our collaboration with NIAID, include provisions that reflect the government’s substantial rights and remedies, many of which are not typically found in commercial contracts, including powers of the government to:

- terminate agreements, in whole or in part, for any reason or no reason;
- reduce or modify the government’s obligations under such agreements without the consent of the other party;
- claim rights, including IP rights, in products and data developed under such agreements;
- audit contract-related costs and fees, including allocated indirect costs;
- suspend the contractor or grantee from receiving new contracts pending resolution of alleged violations of procurement laws or regulations;
- impose U.S. manufacturing requirements for products that embody inventions conceived or first reduced to practice under such agreements;
- suspend or debar the contractor or grantee from doing future business with the government;
- control and potentially prohibit the export of products;
- pursue criminal or civil remedies under the False Claims Act, False Statements Act, and similar remedy provisions specific to government agreements; and
- limit the government’s financial liability to amounts appropriated by the U.S. Congress on a fiscal-year basis, thereby leaving some uncertainty about the future availability of funding for a program even after it has been funded for an initial period.

We may not have the right to prohibit the U.S. government from using certain technologies developed by us, and we may not be able to prohibit third-party companies, including our competitors, from using those technologies in providing products and services to the

U.S. government. The U.S. government generally takes the position that it has the right to royalty-free use of technologies that are developed under U.S. government contracts.

In addition, government contracts and grants, and subcontracts and subawards awarded in the performance of those contracts and grants, normally contain additional requirements that may increase our costs of doing business, reduce our profits, and expose us to liability for failure to comply with these terms and conditions. These requirements include, for example:

- specialized accounting systems unique to government contracts and grants;
- mandatory financial audits and potential liability for price adjustments or recoupment of government funds after such funds have been spent;
- public disclosures of certain contract and grant information, which may enable competitors to gain insights into our research program; and
- mandatory socioeconomic compliance requirements, including labor standards, non-discrimination, and affirmative action programs, and environmental compliance requirements.

Further, under these agreements we are subject to the obligations to and the rights of the U.S. government set forth in the Bayh-Dole Act of 1980 (Bayh-Dole Act). As a result, the U.S. government may have rights in certain inventions developed under these government-funded programs, including a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or nonexclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations, also referred to as “march-in rights.” Any exercise of the march-in rights by the U.S. government could harm our competitive position, business, financial condition, results of operations, and prospects. If the U.S. government exercises such march-in rights, we may receive compensation that is deemed reasonable by the U.S. government in its sole discretion, which may be less than what we might be able to obtain in the open market. IP generated under a government-funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources.

In addition, the U.S. government requires that any products embodying any invention generated through the use of U.S. government-funding be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the IP can show that it made reasonable but unsuccessful efforts to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. manufacturers for products covered by such IP.

As an organization, we are relatively new to government contracting and the related regulatory compliance obligations. If we fail to maintain compliance with those obligations, we may be subject to potential liability and to termination of our contracts.

As a U.S. government contractor, we are subject to financial audits and other reviews by the U.S. government of our costs and performance on their contracts, as well as our accounting and general business practices related to these contracts. Based on the results of its audits, the government may adjust our contract-related costs and fees, including allocated indirect costs. We cannot assure you that future audits and reviews will not have a material adverse impact on our financial condition or results of operations.

Risks related to the commercialization of our pipeline

We have limited sales, distribution, and marketing experience, and have only recently invested significant financial and management resources to establish these capabilities. If we cannot effectively establish such capabilities or enter into agreements with third parties to market and sell our products or to help ensure compliance with local regulatory requirements, our ability to generate revenues may be adversely affected.

Our COVID-19 vaccine is our only commercial product, and we are investing in the development of sales, marketing, distribution, managerial and other non-technical capabilities in and out of the United States, both on our own and with others. We may seek to enter into strategic alliances with other entities to utilize their marketing and distribution capabilities, but may be unable to enter into agreements on favorable terms, if at all. If we rely on third parties to commercialize any approved product, we will receive lower revenues than if we commercialized these products ourselves. In addition, we may have little or no control over the sales efforts of such third parties. If our collaborators do not commit sufficient resources to commercialize our products, and we are unable to develop the necessary marketing capabilities on our own, we may be unable to generate sufficient product revenue to sustain our business.

The commercialization and distribution of our COVID-19 vaccine also subjects us to pharmacovigilance obligations under various regulatory regimes in the jurisdictions where our vaccine is distributed. These regulations generally require us to collect, process,

analyze and monitor safety data and to identify and evaluate adverse reactions to our vaccine as it is administered in those jurisdictions. We partner with third-party organizations to assist us in collecting and processing this safety data as it is reported from healthcare providers, vaccine recipients and others. If we or these third parties cannot comply with relevant regulations, including with respect to the timely processing of safety data, we may be subject to sanctions, increased costs, and reputational harm, or our authorizations to distribute our vaccine in the relevant jurisdiction may be revoked or curtailed. There are a limited number of third-party service providers who are qualified and capable of providing pharmacovigilance services on a global basis, and our inability to identify or contract with them may impede our commercial activities.

We compete with many companies that currently have extensive and well-funded marketing, sales and pharmacovigilance operations, and we must also compete with such companies to recruit, hire, train and retain marketing and sales personnel. We also incur expenses associated with hiring third-party contractors to assist in conducting local pharmacovigilance services. Without a significant internal team or the support of a third party to perform these functions, we may be unable to compete successfully against these more established companies.

The terms of certain of our supply agreements may require us to refund certain prepayments from customers of our COVID-19 vaccine if they reduce purchase commitments or if we fail to deliver the purchased volume.

Some customers for our COVID-19 vaccine prepay us for a portion of the product payment for the vaccine doses that they expect to receive from us. Such prepayments can be substantial. We are generally not required by our contracts to retain these prepayments in cash or otherwise and we generally use them to make capital expenditures and fund the manufacturing scale-up and commercialization of our vaccine. Under certain supply agreements, if we fail to deliver a portion or all of the committed number of doses by a certain date, or if we are unable to successfully obtain regulatory authorization or approval for the commercialization of the vaccine in the relevant jurisdiction, a customer may reduce the volume of vaccine doses that it commits to purchase or terminate the contract. Upon termination, we would generally be required to refund a portion of that customer's prepayment. We may not have the cash or other available resources to satisfy that repayment obligation. In this situation, our business, financial condition, results of operations, and reputation could be materially and adversely affected. Furthermore, if customers do not prepay us for our services in the future, we may have to find other sources of funding, which may not be available when needed or on acceptable terms.

The commercial success of any current or future investigational medicine, if approved, will depend on the degree of market acceptance by physicians, patients, third-party payors, and others in the medical community.

Ethical, social, and legal concerns about genetic research could result in additional regulations restricting or prohibiting the products and processes we may use, including new areas of research such as in gene editing. Additionally, the commercial success of our products will depend in part on the medical community, patients, and third-party or governmental payors accepting mRNA medicines, and our products in particular, as medically useful, cost-effective, and safe. The degree of market acceptance of our investigational medicines, if approved for commercial sale, will depend on numerous factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the ability to offer our products, if approved, at competitive prices;
- the prevalence and severity of any side effects, including any limitations, restrictions (including for use together with other medicines) or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from checkpoint inhibitors or other products or therapies with which our products are co-administered;
- relative convenience and ease of administration;
- the willingness of the target patient population to try, and physicians to prescribe, new therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement, and patients' willingness to pay out-of-pocket in the absence of third-party coverage or adequate reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will be unknown until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the products may require significant resources, especially due to the complexity and uniqueness of our programs, and may never be successful.

We are subject to the risks of doing business outside of the United States.

Because we market our COVID-19 vaccine, and plan to market other products, if approved, and to conduct manufacturing activities outside of the United States, our business is subject to risks associated with doing business outside of the United States. We have limited experience as a company operating outside the United States. We are not permitted to market or promote any of our developmental candidates or investigational medicines before we receive regulatory approval or other authorization from an applicable authority, and we may never receive such approval for any of our developmental candidates or investigational medicines. To obtain separate regulatory approval in many other countries, we must comply with numerous and varying regulatory requirements regarding safety and efficacy and governing, among other things, clinical trials, manufacturing, commercial sales, pricing and distribution of our developmental candidates and investigational medicines, and we cannot predict success in these jurisdictions. We are rapidly expanding our global operations, establishing commercial subsidiaries, and entering into arrangements to support the worldwide manufacture and distribution of our COVID-19 vaccine and other medicines, including with third parties, which is a complex task that we are undertaking on an accelerated timeline. Accordingly, our business and financial results may be adversely affected due to a variety of factors associated with our expanding global business, including:

- efforts to develop an international commercial sales, marketing, and supply chain and distribution organization, including efforts to mitigate longer accounts receivable collection times, longer lead times for shipping, and potential language barriers; for example, in the second half of 2021, we felt the impact of longer delivery lead times for international shipments and exports, which shifted certain anticipated deliveries of our COVID-19 vaccine from 2021 to 2022;
- our customers' ability to obtain reimbursement for our products in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- changes in a specific country's or region's political and cultural climate or economic condition, including as a result of the COVID-19 pandemic;
- an increased legal and compliance burden to establish, maintain and operate legal entities in foreign countries;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, including the European General Data Protection Regulation 2016/679 (GDPR);
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute, and the difficulty of effective enforcement of contractual provisions in local jurisdictions, and the existence of potentially relevant third-party IP rights;
- inadequate IP protection in foreign countries, and the existence of potentially relevant third-party IP rights;
- trade-protection measures including trade restrictions, import or export licensing requirements such as Export Administration Regulations promulgated by the U.S. Department of Commerce and fines, penalties, or suspension or revocation of export privileges, the imposition of government controls, and changes in tariffs;
- the effects of applicable foreign tax structures and potentially adverse tax consequences; and
- significant adverse changes in foreign currency exchange rates.

We are also subject to extensive federal, state and foreign anti-bribery regulations, including the U.S. Foreign Corrupt Practices Act (FCPA), the U.K. Bribery Act, and similar laws in other countries. Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Various laws, regulations and executive orders also restrict the use and dissemination outside the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. As we expand our presence outside the United States, we will need to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside the United States, which could limit our growth potential and increase our development costs.

We cannot guarantee that we, or our employees, consultants, or third-party contractors, are or will be in compliance with all federal, state, and foreign regulations regarding bribery and corruption. Moreover, our strategic collaborators and third-party contractors outside the United States may have inadequate compliance programs or fail to respect the laws and guidance of the territories in which they operate, which may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions. Even if we are not determined to have violated these laws, government investigations typically require the expenditure of significant resources and generate negative publicity, which could adversely affect our business, financial condition, and results of operations.

Sales of pharmaceutical products depends on the availability and extent of reimbursement from third-party payors, and changes to such reimbursement may materially harm our business, prospects, operating results, and financial condition.

Third-party payor coverage and reimbursement for our COVID-19 vaccine is not currently available and there is no guarantee payors will provide coverage and reimbursement for the vaccine in the future. Even if coverage is provided, we may not be able to establish or maintain pricing sufficient to realize a sufficient return on our investment. While coverage is expected to be provided under Medicare Part B, it is unclear to what extent other payors, including certain federal entitlement programs, such as the Vaccines for Children Program, will provide coverage for the product. Additionally, it is uncertain whether any combination respiratory vaccine we develop, if approved, would qualify for coverage under Medicare Part B.

In addition, sales of pharmaceutical products in general depends, to a significant extent, on adequate coverage, pricing and reimbursement from third-party payors. When a new product is approved, the availability and extent of government and private reimbursement, and the pricing, for that product may be uncertain. Pricing and reimbursement for any product we develop may be adversely affected by a number of factors, including:

- changes in, and implementation of, federal, state or foreign government regulations or private third-party payors' reimbursement policies;
- pressure by employers on private health insurance plans to reduce costs; and
- consolidation and increasing assertiveness of payors seeking price discounts or rebates in connection with the placement of our products on their formularies and, in some cases, the imposition of restrictions on access or coverage of particular drugs or pricing determined based on perceived value.

Our ability to set the price for any product we develop will vary significantly from country to country. Our inability to obtain and maintain adequate prices in a particular country may limit the revenues from our products within that country and adversely affect our ability to secure acceptable prices in existing and potential new markets, which may limit market growth. This may create the opportunity for third-party cross-border trade or influence our decision to sell or not to sell a product, thus adversely affecting our geographic expansion plans and revenues.

Drug prices are under significant scrutiny in many countries. We expect drug pricing and other health care costs to continue to be subject to intense political and societal pressures on a global basis. Competition may negatively impact our ability to maintain pricing and our market share. New products marketed by competitors could cause our revenues to decrease due to potential price reductions and lower sales volumes. Additionally, the introduction of competing versions of our products or products approved under abbreviated regulatory pathways may reduce the price that we are able to charge for our products and lower our sales volume.

Many payors continue to adopt benefit plan changes that shift a greater portion of prescription costs to patients, including more limited benefit plan designs, higher patient co-pay or co-insurance obligations and limitations on patients' use of commercial manufacturer co-pay payment assistance programs. Significant consolidation in the health insurance industry has resulted in a few large insurers and pharmacy benefit managers exerting greater pressure in pricing and usage negotiations with drug manufacturers, significantly increasing discounts and rebates required of manufacturers and limiting patient access and usage. Further consolidation among insurers, pharmacy benefit managers and other payors would increase the negotiating leverage such entities have over us and other drug manufacturers. Additional discounts, rebates, coverage or plan changes, restrictions or exclusions as described above could have a material adverse effect on sales of our affected products. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is: a covered benefit under its health plan; safe, effective and medically necessary; appropriate for the specific patient; cost-effective; and neither experimental nor investigational.

Additionally, target patient populations for some of our investigational medicines, including for rare genetic diseases, may be small, and some of our investigational medicines, like PCV, require individual customization. The pricing and reimbursement of our medicines, if approved, must be adequate to support commercial infrastructure. If we cannot obtain adequate levels of reimbursement, we may be unable to successfully market and sell our investigational medicines. The manner and level at which reimbursement is provided for services related to our investigational medicines (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products.

Our failure to obtain or maintain adequate coverage, pricing or reimbursement for our products could have an adverse effect on our business, reputation, revenues and results of operations.

Recent federal legislation and actions by federal, state and local governments may permit reimportation of drugs from foreign countries into the United States, including foreign countries where the drugs are sold at lower prices than in the United States, which could materially adversely affect our operating results.

We may face competition in the United States for our development candidates and investigational medicines, if approved, from therapies sourced from foreign countries with price controls on pharmaceutical products. For example, in October 2020, the FDA published a final rule that would allow for the importation of certain prescription drugs from Canada, where there are government price controls. Since the issuance of the final rule, several industry groups filed federal lawsuits requesting injunctive relief to prevent the rule from taking effect and challenging multiple aspects of the final rule. This litigation has not progressed and the market implications are currently unknown, but legislation or regulations allowing the reimportation of drugs, if enacted, could decrease the price we receive for any products we may develop and adversely affect our future revenues and potential profitability.

Healthcare legislative reform discourse and potential or enacted measures may have a material adverse impact on our business and results of operations and legislative or political discussions surrounding the desire for and implementation of pricing reforms may adversely impact our business.

In the United States, federal and state legislatures, health agencies and third-party payors continue to focus on containing the cost of health care. Legislative and regulatory proposals, enactments to reform health care insurance programs and increasing pressure from social sources could significantly influence the manner in which our products, if approved, are prescribed and purchased. For example, provisions of the ACA have resulted in changes in the way health care is paid for by both governmental and private insurers, including increased rebates owed by manufacturers under the Medicaid Drug Rebate Program, annual fees and taxes on manufacturers of certain branded prescription drugs, the requirement that manufacturers participate in a discount program for certain outpatient drugs under Medicare Part D and the expansion of the number of hospitals eligible for discounts under Section 340B of the PHSA. See the section titled "Business—Government Regulation—Current and future healthcare reform legislation."

We may face uncertainties as a result of efforts to repeal, substantially modify or invalidate some or all of the provisions of the ACA. There is no assurance that the ACA, as currently enacted or as amended in the future, will not adversely affect our business and financial results, and we cannot predict how future federal or state legislative or administrative changes relating to healthcare reform will affect our business.

There is increasing public attention on the costs of prescription drugs and there have been, and are expected to continue to be, legislative proposals to address prescription drug pricing, which could have significant effects on our business. These actions and the uncertainty about the future of the ACA and healthcare laws may put downward pressure on pharmaceutical pricing and increase our regulatory burdens and operating costs.

There is also significant economic pressure on state budgets, including as a result of the COVID-19 pandemic, that may result in states increasingly seeking to achieve budget savings through mechanisms that limit coverage or payment for drugs. In recent years, some states have considered legislation and ballot initiatives that would control the prices of drugs, including laws to allow importation of pharmaceutical products from lower cost jurisdictions outside the United States and laws intended to impose price controls on state drug purchases. State Medicaid programs are increasingly requesting manufacturers to pay supplemental rebates and requiring prior authorization by the state program for use of any drug for which supplemental rebates are not being paid. Government efforts to reduce Medicaid expenses may lead to increased use of managed care organizations by Medicaid programs. This may result in managed care organizations influencing prescription decisions for a larger segment of the population and a corresponding limitation on prices and reimbursement for our products, if approved.

In the EU and some other international markets, the government provides health care at low cost to consumers and regulates pharmaceutical prices, patient eligibility or reimbursement levels to control costs for the government-sponsored health care system. Many countries have announced or implemented measures, and may in the future implement new or additional measures, to reduce health care costs to limit the overall level of government expenditures. These measures vary by country and may include, among other things, patient access restrictions, suspensions on price increases, prospective and possible retroactive price reductions and other recoupments and increased mandatory discounts or rebates, recoveries of past price increases and greater importation of drugs from lower-cost countries. These measures may adversely affect our revenues and results of operations.

If the market opportunities for our programs, development candidates or investigational medicines are smaller than we believe they are, or we are unable to successfully identify clinical trial participants, our revenue may be adversely affected and our business may suffer.

We focus certain of our research and product development activities on treatments for severe rare genetic diseases, where the patient populations are difficult to ascertain or small. Additionally, we expect to initially seek approval of our PCV and intratumoral immuno-oncology investigational medicines for use by patients with relapsed or refractory advanced disease, i.e., the populations the FDA often approves new therapies for initially. If any such medicines prove to be sufficiently beneficial, we would expect to seek approval in earlier lines of treatment and potentially as a first line therapy. There is no guarantee that our investigational medicines, even if approved, would be approved for earlier lines of therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

Our projections of both the number of people who have these diseases, as well as the subset of those who have the potential to benefit from treatment with our investigational medicines, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of trial participants, both in and outside the United States, may be lower than expected and potential clinical trial participants or patients may not be otherwise amenable to treatment with our investigational medicines or products, or new clinical trial participants or patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business. Even if we obtain significant market share for our products, if approved, because the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

The illegal distribution and sale by third parties of counterfeit or stolen versions of mRNA products, or the unauthorized donation or re-sale of mRNA products, could have a negative impact on our financial performance or reputation.

Third parties could illegally distribute and sell, especially online, counterfeit versions of mRNA products that do not meet the rigorous cGMP manufacturing and testing standards. Counterfeit products are frequently unsafe or ineffective, and could be life-threatening. Counterfeit medicines may contain harmful substances or the wrong dose. However, to distributors and users, counterfeit products may be visually indistinguishable from the authentic version.

Reports of adverse reactions to counterfeit products, increased levels of counterfeiting, or unsafe mRNA products could materially affect patient confidence in our mRNA products. It is possible that adverse events caused by unsafe counterfeit or other non-mRNA products will mistakenly be attributed to our mRNA products. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels could adversely impact patient safety, our reputation, and our business. Public loss of confidence in the integrity in mRNA products as a result of counterfeiting, theft, or improper manufacturing processes could have a material adverse effect on our business, results of operations, and financial condition.

Further, the unauthorized donation or resale of our product could adversely affect our ability to sell in a particular territory, and have other adverse effects on our business, results of operations, and financial condition.

Risks related to our finances

We have a limited history of recognizing revenue from product sales and may not be able to achieve or maintain long-term sustainable profitability.

Before the year ended December 31, 2021, we incurred net losses in each year since our inception. Other than for our COVID-19 vaccine, we have not completed pivotal clinical trials for any of our programs, and it may be years for most of our investigational medicines, if ever, before we or our strategic collaborators have a product ready for commercialization. Our ability to generate revenue and maintain profitability depends on our ability, alone or with strategic collaborators, to successfully complete the development of and obtain the regulatory approvals necessary to commercialize our products and investigational medicines, including commercializing our COVID-19 vaccine, which is subject to numerous risks.

We have incurred, and expect to continue to incur, significant costs associated with the commercialization of our COVID-19 vaccine and our clinical and preclinical development activities. We may not be able to achieve or maintain long-term sustainable profitability and may need to obtain additional funding to continue operations.

We anticipate that our expenses will increase substantially if and as we:

- continue or expand our research or development of our programs in preclinical development;
- initiate additional preclinical, clinical, or other studies for our development candidates and investigational medicines, including under our strategic alliance agreements;
- continue to invest in our platform to conduct research to identify novel mRNA technology improvements, including to identify methods of mRNA delivery, such as improvements to our LNPs;
- change or add to internal manufacturing capacity or capability, or additional manufacturers or suppliers;
- add additional infrastructure to our quality control and quality assurance groups to support our operations as we progress our investigational medicines toward commercialization;
- attract and retain skilled personnel;
- create additional infrastructure to support our product development and planned future commercialization efforts, including new sites in the United States and abroad;
- seek marketing approvals and reimbursement for our investigational medicines;
- establish a sales, marketing, and distribution infrastructure to commercialize any products;

- acquire or in-license other development candidates, investigational medicines, and technologies;
- make milestone or other payments under any in-license agreements; and
- experience any delays or encounter issues with any of the above.

Our quarterly and annual operating results may fluctuate. As a result, we may fail to meet or exceed the expectations of research analysts or investors, which could cause our stock price to decline and negatively impact our financing or funding ability as well as negatively impact our ability to exist as a standalone company.

Our financial condition and operating results have varied in the past and will continue to fluctuate from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. As such, a period-to-period comparison of our operating results may not be a good indication of our future performance. In any particular quarter, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline. Factors relating to our business that may contribute to these fluctuations include the following, as well as other factors described in these *Risk Factors* and elsewhere in this Annual Report on Form 10-K:

- our ability to manufacture and deliver supply of our COVID-19 vaccine;
- variations in our financial results, development timelines or recommendations by securities analysts, or those of companies that are perceived to be similar to us;
- delays or failures in advancement of existing or future development candidates into the clinic or investigational medicines in clinical trials;
- the feasibility of developing, manufacturing, and commercializing our programs;
- the outcomes of research programs, clinical trials (including any adverse safety events), or other product development or approval processes conducted by us and our strategic collaborators;
- the timing of disclosure of any milestones related to any of our programs that are managed by our strategic collaborators or competitors;
- our ability to consistently manufacture our development candidates and investigational medicines;
- our ability to accurately report our financial results in a timely manner; and
- our ability to obtain, protect, and enforce our IP rights, as well as our know-how and technologies.

The investment of our cash, cash equivalents, and investments is subject to risks which may cause losses and affect the liquidity of these investments.

As of December 31, 2021, we had approximately \$17.6 billion in cash, cash equivalents, and investments, which are subject to general credit, liquidity, market, inflation and interest rate risks. We may realize losses in the fair value of these investments. In addition, if our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. These and other market risks associated with our investment portfolio may adversely affect our results of operations, liquidity, and financial condition.

Risks related to our business and operations

We may encounter difficulties in managing the development and expansion of our company, which could disrupt our operations.

As of December 31, 2021, we had approximately 2,700 full-time employees and, in connection with the growth and advancement of our pipeline and commercialization of our company, we expect to increase the number of employees and the scope of our operations. To manage such development and expansion, including internationally, we must continue to implement and improve our managerial, operational, and financial systems, expand our facilities, and recruit and train qualified personnel. Our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities.

We are pursuing development candidates and investigational medicines in many therapeutic areas and across a wide range of diseases. Successfully developing products for and fully understanding the regulatory and manufacturing pathways to all of these therapeutic areas and diseases requires significant depth of talent, resources, and corporate processes in order to allow simultaneous execution across multiple areas. We may not be able to effectively manage this simultaneous execution and the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees, and reduced productivity among remaining employees. The physical expansion of our operations, including the construction of the Moderna Science Center in Cambridge, the expansion of our Norwood campus and the construction of manufacturing facilities overseas, may lead to significant costs and may divert financial resources from other projects, such as the development of our investigational medicines. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to

commercialize our COVID-19 vaccine, or our other investigational medicines, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

Our failure to upgrade and maintain our enterprise resource planning system (ERP) could adversely impact our business and results of operations.

We are working to upgrade our global ERP system to support our anticipated future growth and expansion as a commercial operation. We expect to incur substantial costs in implementing our ERP system, and any disruptions or difficulties in implementing or using our ERP system could adversely affect our controls, resulting in harm to our business, including our ability to forecast or make sales and collect our receivables. Significant delays in documenting, reviewing and testing our internal control could cause us to fail to comply with our SEC reporting obligations related to our management's assessment of our internal control over financial reporting. Moreover, such disruptions or difficulties could result in unanticipated costs and diversion of management attention.

Our success depends on our ability to retain key employees, consultants, and advisors and to attract, retain, and motivate qualified personnel.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends on our ability to attract and retain highly qualified managerial, scientific, technical, quality-control, manufacturing, medical and commercial personnel. We are highly dependent on members of our management and scientific teams. Each of our executive officers and employees, including key scientists and clinicians, are employed "at will," meaning we or each officer or employee may terminate the employment relationship at any time. The loss of any of these persons' services may adversely impact the achievement of our research, development, financing, and commercialization objectives. We do not have "key person" insurance on any of our employees. Several of our key employees, including members of our executive team, have been with us for a long period of time, and have valuable, fully vested stock options or other long-term equity incentives. We may not be able to retain these employees due to the competitive environment in the biotechnology industry, particularly in Cambridge, Massachusetts.

In addition, we rely on consultants, contractors, and advisors, including scientific and clinical advisors, to assist us in formulating our research and development, regulatory approval, manufacturing and commercialization strategies. These individuals may be employed by other employers and may have commitments under contracts with others that may limit their availability to us. The loss of the services of one or more of our current employees or advisors might impede the achievement of our research, development, regulatory approval, manufacturing and commercialization objectives. In addition, we have flexibly grown our workforce through the use of contractors and part time workers. If we cannot retain the services of such personnel, we could experience delays in the operation of our business.

Competition for skilled personnel, including in mRNA and LNP research, clinical operations, regulatory affairs, therapeutic area management, and manufacturing, is intense and the turnover rate is high. We may be unable to attract and retain personnel on favorable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. In some instances, failure to attract and retain personnel could result in delays in production or difficulties in maintaining compliance with regulatory requirements. In addition, adverse publicity, failure to succeed in preclinical or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. We may also be unable to attract and retain highly qualified sales and marketing professionals to support our COVID-19 vaccine and any future products. The inability to recruit, or loss of services of certain executives, key employees, consultants, or advisors, may impede the progress of our research, development and global commercialization objectives and adversely impact our business, financial condition, results of operations, and prospects.

If we cannot maintain our corporate culture, we could lose the innovation, teamwork and passion that we believe contribute to our success, and our business may be harmed.

We invest substantial time and resources in building and maintaining our culture and developing our personnel; however, as we continue to expand, it may be increasingly difficult to maintain our culture. Throughout the COVID-19 pandemic, much of our workforce has worked remotely and we implemented remote hiring and onboarding programs to facilitate significant hiring during 2021 in a remote work environment. The dramatic growth of our workforce, coupled with shifts in workplace and workstyle, increase the risk of our ability to maintain culture. Any failure to preserve our culture could negatively affect our future success, including our ability to retain and recruit personnel and to effectively pursue our strategic plans.

Our internal computer systems and physical premises, or those of third parties with which we share sensitive data or information, may fail or suffer security breaches, which could materially disrupt our product development programs and manufacturing operations.

Our internal computer systems and those of our current and any future strategic collaborators, vendors, contractors, consultants or regulatory authorities with whom we share sensitive data or information are vulnerable to damage from computer viruses, unauthorized access, natural disasters (which may become more frequent in the future as a result of climate change), terrorism, cybersecurity threats, war, and telecommunication and electrical failures. We have experienced, and may experience in the future, cyber-attacks on our information technology systems by threat actors of all types (including nation states, criminal enterprises, individual actors and/or advanced persistent threat groups). In addition, we may experience intrusions on our physical premises by any of these threat actors. If any such cyber-attack or physical intrusion were to cause interruptions in our operations, such as a material disruption of our development programs or our manufacturing operations, or due to a loss of any of our proprietary information, it would have a material and adverse effect on us. For example, the loss of clinical trial data from one or more clinical trials could cause delays in our regulatory approval efforts and increase our costs to recover or reproduce the data. In addition, because we run multiple clinical trials in parallel, any breach of our computer systems or physical premises may result in a loss of data or compromised data integrity across many of our programs in many stages of development. Our cybersecurity liability insurance may not cover all damages we would sustain based on any breach of our computer security protocols or cybersecurity attack.

Any data breach, security incident loss, or compromise of personal information, including any clinical trial participant personal data may also subject us to civil fines and penalties, or claims for damages either under the GDPR and relevant member state law in the EU, other foreign laws, and the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), and other relevant state and federal privacy laws in the United States including the California Consumer Privacy Act (the CCPA). We have from time to time received information that companies working on vaccine research and development may be a particular focus for those planning cyberattacks. For example, on May 13, 2020, the Federal Bureau of Investigation (FBI) and Cybersecurity and Infrastructure Security Agency (CISA), announced that the FBI was investigating the targeting and compromise of U.S. organizations conducting COVID-19-related research by People's Republic of China, or PRC-affiliated cyber actors. Furthermore, on July 16, 2020, the National Security Agency and other U.S. and foreign agencies released a joint cybersecurity advisory regarding the Russian Intelligence Services' targeting of COVID-19 research and vaccine development. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, including but not limited to information related to the research and manufacturing of our COVID-19 vaccine and/or other vaccines, we could incur liability, our competitive and reputational position could be harmed, and the further development and commercialization of our investigational medicines could be delayed. With respect to potential liability for breaches involving personal information, the CCPA is of particular concern since it provides for a private right of actions for certain personal information breaches.

We may use our financial and human resources to pursue a particular research program or investigational medicine and fail to capitalize on programs or investigational medicines that may be more profitable or for which there is a greater likelihood of success.

We pursue and fund the development of selected research programs or investigational medicines and may choose to forego or delay pursuit of opportunities with other programs or investigational medicines that could later prove to have greater commercial potential. For example, we have focused a significant amount of resources on our COVID-19 vaccine since the commencement of the COVID-19 pandemic. Our resource allocation decisions, or our contractual commitments to provide resources to our strategic collaborators, may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for investigational medicines may not yield commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular investigational medicine, we may relinquish valuable rights to that investigational medicine through a strategic alliance, licensing, or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such investigational medicine, or we may allocate internal resources to an investigational medicine in a therapeutic area in which it would have been more advantageous to enter into a strategic alliance.

If we are not successful in discovering, developing, and commercializing additional products beyond our current portfolio, our ability to expand our business and achieve our strategic objectives would be impaired.

A key element of our strategy is to discover, develop, and potentially commercialize additional products beyond our current portfolio to treat various conditions and in a variety of therapeutic areas. We intend to do so by investing in our own drug discovery efforts, exploring potential strategic alliances for the development of new products, and in-licensing technologies. Identifying new investigational medicines requires substantial technical, financial, and human resources. We may fail to identify promising investigational medicines and, even if we do identify such medicines, we may fail to successfully develop and commercialize products for many reasons, including:

- competitors may develop alternatives that render our investigational medicines obsolete;
- investigational medicines we develop may be covered by third parties' patents or other exclusive rights;
- an investigational medicine may, on further study, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;

- we may be incapable of producing an investigational medicine in commercial quantities at an acceptable cost, or at all; and
- an approved product may not be accepted as safe and effective by patients, the medical community or third-party payors.

If we are unsuccessful in identifying and developing additional products, our potential for growth may be impaired.

Our business could be harmed if we suffer damage to our reputation, including as a result of a product recall.

The FDA and similar foreign governmental authorities have the authority to require the recall of certain commercialized products. In the case of the FDA, the authority to require a recall of a biologic product must be based on an FDA finding that a batch, lot of other quantity of the biologic product presents an imminent or substantial hazard to the public health. In addition, foreign governmental bodies have the authority to require the recall of any investigational medicine in the event of material deficiencies or defects in design or manufacture. Manufacturers may, under their own initiative, recall a product if any material deficiency in a product is found. A government-mandated or voluntary recall by us or our strategic collaborators could occur as a result of manufacturing errors, design or labeling defects or other deficiencies and issues, as occurred with the recall of certain batches of our COVID-19 vaccine shipped to Japan that were found to contain foreign particulate. Recalls of any of our products would divert managerial and financial resources and have an adverse effect on our financial condition and results of operations. A recall announcement could harm our reputation with customers and negatively affect our sales. Our reputation could be further impacted by public discourse regarding our business and the perception of our business strategy.

Product liability lawsuits against us could cause us to incur substantial liabilities and limit commercialization of any product or investigational medicine that we may develop, such as our COVID-19 vaccine.

We are exposed to product liability risk related to the development, testing, manufacturing and marketing of our COVID-19 vaccine and our investigational medicines in clinical trials. Product liability claims and related cross-claims and claims for indemnification may be brought against us by patients, healthcare providers or others using, prescribing, selling or otherwise coming into contact with our COVID-19 vaccine or investigational medicines. For example, we may be sued if the COVID-19 vaccine or any investigational medicine allegedly causes injury or is found to be otherwise unsuitable during clinical trials, manufacturing, or, if approved, marketing, sale or commercial use. If we cannot successfully defend ourselves against such claims, we could incur substantial liabilities.

We could also face product liability claims relating to the worsening of a patient's condition, injury or death alleged to have been caused by one of our COVID-19 vaccine or investigational medicines. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, knowledge of risks, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. Such claims might not be fully covered by product liability insurance. If we succeed in marketing products, including our COVID-19 vaccine, product liability claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, suspension or withdrawal of approvals or license revocation. Regardless of the merits or eventual outcome, liability claims may result in decreased demand for our products, injury to our reputation and significant negative media attention, costs to defend the related litigation, withdrawal of clinical trial participants, loss of revenue, a diversion of management's time and our resources, substantial monetary awards to trial participants, patients or their family members, payments to indemnify clinical trial sites and other clinical trial partners, and a decline in our stock price.

We are also exposed to liabilities that are unique to developing and commercializing an mRNA vaccine during an ongoing global pandemic. Although the U.S. and certain foreign governments have contractually agreed to indemnify us or make statutory immunity available to us, such indemnification or statutory immunity may not be available to cover potential claims or liabilities resulting from the research, development, manufacture, distribution or commercialization of our COVID-19 vaccine. Additionally, other foreign government that we contract with in the future may not provide us with similar contractual indemnity or statutory immunity. Substantial claims arising from the vaccine outside the scope of or in excess of U.S. or foreign government indemnity or statutory immunity could harm our financial condition and operating results. Moreover, any adverse event or injury for which we are liable, even if fully covered under an indemnity or immunity, could negatively affect our reputation.

We may not be able to maintain our product liability insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. While our current insurance program includes coverage for the sale of commercial products for when we obtain marketing approval for our medicines, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in individual, mass tort and class-action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and could adversely affect our results of operations and business.

If the costs of maintaining adequate insurance coverage increase significantly in the future, our operating results could be materially adversely affected. Likewise, if insurance coverage should become unavailable to us or become economically impractical, we would be required to operate our business without indemnity from commercial insurance providers. Additionally, even if we maintain insurance coverage for a type of liability, a particular claim may not be covered if it is subject to a coverage exclusion or we do not otherwise meet the conditions for coverage. If we operate our business with inadequate insurance, we could be responsible for paying claims or judgments against us, which could adversely affect our results of operations or financial condition.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws and false claims laws. If we cannot comply, or have not fully complied, with such laws, we could face substantial penalties.

Healthcare providers, physicians and third-party payors in the United States and elsewhere play a primary role in the recommendation and prescription of pharmaceutical products. Arrangements with third-party payors and customers can expose pharmaceutical manufacturers to broadly applicable fraud and abuse and other healthcare laws and regulations, which may constrain the business or financial arrangements and relationships through which such companies sell, market and distribute pharmaceutical products. In particular, the promotion, sales and marketing of healthcare items and services, as well as a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials. See the section entitled “Business—Government Regulation—Other healthcare laws.”

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, is time- and resource-consuming and can divert a company’s attention from the business. If our operations are found to violate any of these laws or any other regulations that apply to us, we may be subject to significant sanctions, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, reputational harm, exclusion from participation in federal and state funded healthcare programs, contractual damages and the curtailment or restricting of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance. Furthermore, if any physician or other healthcare provider or entity with whom we do business is found to be not in compliance with applicable laws, they may be subject to similar penalties. Any action for violation of these laws, even if successfully defended, could cause us to incur significant legal expenses and divert management’s attention from the operation of the business. In addition, the approval and commercialization of any product candidate we develop outside the United States will subject us to foreign healthcare laws.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the EU and the U.K. The provision of benefits or advantages to induce or reward improper performance generally is also governed by the national anti-bribery laws of EU Member States, and the U.K. Bribery Act 2010 in the U.K. Infringement of these laws could result in substantial fines and imprisonment. The EU Directive (2001/83/EC, as amended) governing medicinal products for human use provides that, where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy. This provision has been transposed into the Human Medicines Regulations 2012 and so remains applicable in the U.K. despite its departure from the EU.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often are the subject of prior notification and approval by the physician’s employer, his or her competent professional organization, or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

We are subject to various and evolving laws and regulations governing the privacy and security of personal data, and our failure to comply could adversely affect our business, result in fines and/or criminal penalties, and damage our reputation.

Privacy and data security have become significant issues in the United States, Europe and in many other jurisdictions in which we operate and/or collect personal information. We are subject to data privacy and security laws and regulations in various jurisdictions that apply to the collection, storage, use, sharing and security of personal data, including health information, and impose significant compliance obligations. In addition, numerous other federal and state laws, including state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use, disclosure and security of personal information. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing focus on privacy and data protection issues.

For example, the GDPR has imposed stringent obligations on us with respect to our processing personal data and the cross-border transfer of such data, including higher standards of obtaining consent, more robust transparency requirements, data breach notification requirements, requirements for contractual language with our data processors, and stronger individual data rights. Different EEA Member States have interpreted the GDPR differently and many have imposed additional requirements, adding to the complexity of processing personal data in the EEA. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EEA that are not considered to provide “adequate” protection to personal data, including the United States, and permits data protection authorities to impose large penalties for violations. Compliance with the GDPR is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices. Despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with any activities falling within the scope of the GDPR.

In the United States, California has passed the California Consumer Privacy Act and several other states and the federal government are actively considering proposed legislation governing the protection of personal data. Additionally, Brazil passed the General Data Protection Law, which went into effect in August 2020. Data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges. Each law is also subject to various interpretations by courts and regulatory agencies, creating additional uncertainty, and our efforts to comply with the evolving data protection rules may be unsuccessful.

We must devote significant resources to understanding and complying with the changing landscape in this area. Failure to comply with data protection laws may expose us to risk of enforcement actions taken by authorities, private rights of action in some jurisdictions, and potential significant penalties if we are found to be non-compliant. Failure to comply with the GDPR and applicable national data protection laws of EEA member states could lead to substantial fines. Some of these laws and regulations also carry the possibility of criminal sanctions. For example, we could be subject to penalties, including criminal penalties, if we knowingly obtain or disclose individually identifiable health information from a HIPAA-covered health care provider or research institution that has not complied with HIPAA’s requirements for disclosing such information. Furthermore, the number of government investigations related to data security incidents and privacy violations continues to increase and government investigations typically require significant resources and generate negative publicity, which could harm our business and our reputation.

The COVID-19 pandemic has added further complexity to the processing of personal data. For example, safety measures intended to protect our employees, contractors, and other visitors to our sites may require the collection of certain personal data. Our efforts to protect personal data may be unsuccessful and we could unintentionally be subject to unauthorized access or disclosure of such personal data.

The Clinical Trials Regulation (EU) No. 536/2014 (the Clinical Trial Regulation) and the EMA policy on publication of clinical data for medicinal products for human use both permit the EMA to publish clinical information submitted in MAAs. The ability of third parties to review and/or analyze data from our clinical trials may increase the risk of commercial confidentiality breaches and result in enhanced scrutiny of our clinical trial results. Such scrutiny could result in public misconceptions regarding our drugs and drug candidates. These publications could also result in the disclosure of information to our competitors that we might otherwise deem confidential, which could harm our business.

Certain aspects of our business may be adversely affected by the ongoing COVID-19 pandemic.

Certain of our clinical trials have been adversely affected by the ongoing COVID-19 pandemic, resulting in paused enrollment or delayed site initiations. Site initiation, participant recruitment and enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis may be paused or delayed (or continue to be paused or delayed) due to changes in hospital or university policies, federal, state or local regulations or restrictions, prioritization of hospital resources toward pandemic efforts, travel restrictions, concerns for patient safety in a pandemic environment, or other pandemic-related reasons. As the pandemic persists, some participants and clinical investigators may be unable to comply with clinical trial protocols. For example, many countries have implemented quarantines or travel limitations (whether voluntary or required), which may impede participant movement, affect sponsor access to study sites, or interrupt healthcare services, and we may be unable to conduct our clinical trials.

The COVID-19 pandemic has disrupted and may continue to disrupt the United States’ healthcare and healthcare regulatory systems. Such disruptions could divert healthcare resources away from, or materially delay the review and/or approval by the FDA and other regulatory agencies with respect to, our clinical trials or product approvals, which could materially delay our clinical trials for development candidates or our commercial efforts.

We utilize third parties to, among other things, manufacture raw materials, components, parts, and consumables, perform quality testing and ship our products. We also manufacture our development candidates and investigational medicines and perform various services at our manufacturing facility. Certain of our third-party manufacturers and suppliers may encounter delays in providing their services in response to the COVID-19 pandemic. If either we or any third-party manufacturers or third parties in the supply chain for materials used in the production of our COVID-19 vaccine, development candidates or investigational medicines are adversely

impacted by restrictions resulting from the COVID-19 pandemic, our supply chain may be disrupted, limiting our ability to manufacture our COVID-19 vaccine, as well as investigational medicines for our clinical trials, research and development operations and commercialization. In addition, delays and disruptions experienced by our strategic collaborators due to the COVID-19 pandemic could adversely impact the ability of such parties to fulfill their obligations, which could affect the clinical development or regulatory approvals of development candidates and investigational medicines under joint control.

If we engage in acquisitions, joint ventures, or strategic collaborations, this may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We may complete acquisitions and collaborations, including licensing or acquiring complementary products, IP rights, technologies, or businesses. Any such acquisition, joint venture, or collaboration may entail numerous risks, including:

- increased operating expenses and cash requirements;
- assimilation of operations, IP, and products, including difficulties associated with integrating new personnel;
- the diversion of management's attention from our existing product programs and initiatives;
- the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or investigational medicines and regulatory approvals; and
- our inability to generate revenue from acquired technology or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

If we undertake acquisitions, we may utilize our cash, issue dilutive securities, assume or incur debt obligations, incur large one-time expenses, and acquire intangible assets that could result in significant future amortization expense. Moreover, if we cannot locate suitable acquisition or strategic collaboration opportunities, our ability to grow or obtain access to technology or products that may be important to the development of our business may be impaired.

Risks related to ownership of our common stock

The price of our common stock has been volatile and fluctuates substantially, which could result in substantial losses for stockholders.

Our stock price has been, and is expected to continue to be, subject to substantial volatility. From December 7, 2018, our first day of trading on the Nasdaq Global Select Market, through December 31, 2021, our stock has traded within a range of a high price of \$497.49 and a low price of \$11.54 per share. Since we began our development efforts with respect to our COVID-19 vaccine in early 2020, our stock has experienced pronounced and extended periods of volatility. As a result of the volatility in our stock price, our stockholders could incur substantial losses.

Public statements by us, government agencies, the media, competitors, financial analysts, or others relating to the COVID-19 pandemic and efforts to combat it have in the past resulted, and may in the future result, in significant fluctuations in our stock price. Given the global focus on the COVID-19 pandemic, information in the public arena on this topic, whether or not accurate, has had and will likely continue to have an outsized impact (positive or negative) on our stock price. Information related to our clinical trials, manufacturing, regulatory and commercialization efforts with respect to our COVID-19 vaccine, or information regarding such efforts by competitors, or the evolution of the pandemic, may meaningfully impact our stock price.

The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above your initial purchase price. The market price for our common stock may be influenced by many factors, including:

- the success of our COVID-19 vaccine sales and anticipated product revenue;
- results of clinical trials of our investigational medicines or those of our competitors;
- the success of competitive products or technologies, particularly vaccines or treatments for COVID-19;
- the emergence or decline of new or existing variants of the SARS-CoV-2 virus;
- commencement or termination of strategic alliances;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- expenses related to any of our products, investigational medicines or clinical development programs;
- the results of our efforts to discover, develop, acquire, or in-license additional investigational medicines;

- actual or anticipated changes in estimates of financial results, development timelines, or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry, and market conditions;
- the numerous programs in our pipeline, the development of which could each generate news or significant adverse events that could impact financial results or recommendations by securities analysts;
- announcement by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments; and
- public announcements by us or our strategic collaborators regarding the progress of our development candidates or investigational medicines or similar public announcements by our competitors.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, and results of operations, and prospects.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

As of February 18, 2022, our executive officers, directors, and affiliated stockholders beneficially owned approximately 14% of our outstanding common stock. In addition, non-affiliated five percent or greater stockholders beneficially owned approximately 25% of our outstanding common stock. These stockholders will have the ability to influence us through their ownership positions. For example, if these stockholders were to act together, they could exert significant influence over matters such as elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, by-laws, and Delaware law contain provisions that may have the effect of delaying or preventing a hostile takeover or change in control of us or changes in our management. Our amended and restated certificate of incorporation and amended and restated by-laws include provisions that:

- authorize "blank check" preferred stock, which could be authorized for issuance by our board of directors without stockholder approval and may contain voting, liquidation, dividend, and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter, or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We do not currently intend to declare or pay cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business or to return cash to shareholders through share repurchases. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Our amended and restated by-laws designate the Court of Chancery of the State of Delaware or the United States District Court for the District of Massachusetts as the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

Pursuant to our amended and restated by-laws, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for state law claims for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of or based on a breach of a fiduciary duty owed by any of our current or former directors, officers, or other employees to us or our stockholders, (3) any action asserting a claim against us or any of our current or former directors, officers, employees, or stockholders arising pursuant to any provision of the Delaware General Corporation Law or our amended and restated by-laws, or (4) any action asserting a claim governed by the internal affairs doctrine (the Delaware Forum Provision). The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act or the Exchange Act. Our amended and restated by-laws further provide that the United States District Court for the District of Massachusetts is the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (the Federal Forum Provision). Our amended and restated by-laws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the Delaware Forum Provision and the Federal Forum Provision.

The Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts, as applicable. Additionally, the forum selection clauses in our amended and restated by-laws may limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees, which may discourage the filing of lawsuits against us and our directors, officers, and employees, even though an action, if successful, might benefit our stockholders. While the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court are "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is unenforceable or invalid, and if the Federal Forum Provision is found to be unenforceable, we may incur additional costs in resolving such matters. The Court of Chancery of the State of Delaware and the United States District Court for the District of Massachusetts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

General risk factors

Our employees, principal investigators, and consultants may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators leading our clinical trials, and consultants. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions; provide accurate information to the FDA, the EMA, and other regulatory authorities; comply with healthcare fraud and abuse laws and regulations in the United States and abroad; or report financial information or data accurately or disclose unauthorized activities to us. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and serious harm to our reputation. Sales, marketing, and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing, and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. It is not always possible to identify and deter employee misconduct, and the precautions we take may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations, and prospects, including the imposition of significant fines or other sanctions.

Unfavorable U.S. or global economic conditions could adversely affect our business, financial condition, or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and financial markets, including by the COVID-19 pandemic, or any other health epidemic. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our investigational medicines and our ability to raise additional capital when needed on favorable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Employee litigation and unfavorable publicity could negatively affect our future business.

Our employees may, from time to time, bring lawsuits against us regarding injury, creating a hostile workplace, discrimination, wage and hour disputes, sexual harassment, or other employment issues. In recent years, there has been an increase in the number of discrimination and harassment claims generally. Coupled with the expansion of social media platforms and similar devices that allow individuals access to a broad audience, these claims have had a significant negative impact on some businesses. Certain companies that have faced employment- or harassment-related lawsuits have had to terminate management or other key personnel, and have suffered reputational harm that has negatively impacted their business. Any employment-related claim could negatively affect our business.

If we fail to comply with environmental, health, and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health, and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment, and disposal of hazardous and flammable materials and wastes, including chemicals and biological materials. We generally contract with third parties for the disposal of these hazardous materials and waste products, and we cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from any use by us of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological or hazardous materials.

In addition, we may incur substantial costs to comply with current or future environmental, health, and safety laws and regulations. These laws and regulations may impair our research, development, or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Changes in tax law could adversely affect our business and financial condition.

We are subject to evolving and complex tax laws in the jurisdictions in which we operate. The rules dealing with U.S. federal, state, and local and non-U.S. income taxation are constantly under review by legislative and tax authorities. Changes to tax laws (which changes may have retroactive application) could adversely affect us and our stockholders. In recent years, such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

The increasing use of social media platforms presents new risks and challenges.

Social media is increasingly being used to communicate about our research, development candidates, investigational medicines, and the diseases our development candidates and investigational medicines are being developed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear. This uncertainty creates risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us. For example, subjects may use social media channels to comment on their experience in an ongoing blinded clinical trial or to report an alleged adverse event. When such disclosures occur, we may fail to monitor and comply with applicable adverse event reporting obligations or we may not be able to defend our business or the public's legitimate interests in the face of the political and market pressures generated by social media due to restrictions on what we may say about our development candidates and investigational medicines. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions, or incur other harm to our business.

Item 1B - Unresolved Staff Comments

None.

Item 2. Properties

We have two campuses in Massachusetts. We occupy a multi-building campus in Cambridge, Massachusetts (Cambridge campus), consisting of a mix of offices and research laboratory space totaling approximately 261,000 square feet. The Cambridge campus is the location of our corporate headquarters, platform, drug discovery and clinical development. The Cambridge campus is leased with the majority of the space being leased through 2029.

The Moderna Technology Center (MTC campus) is located in Norwood, Massachusetts and is comprised of three buildings (MTC South, MTC North and MTC East). MTC South is approximately 200,000 square feet. MTC North is approximately 200,000 square feet and provides lab and office space, directly supporting improvement in our manufacturing capabilities. MTC East is approximately 240,000 square feet for expansion of our commercial and clinical activities. The MTC campus is leased through 2042 and we have the option to extend it for three five-year terms.

We also lease other office and lab spaces globally for our business operations.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market for Our Common Stock

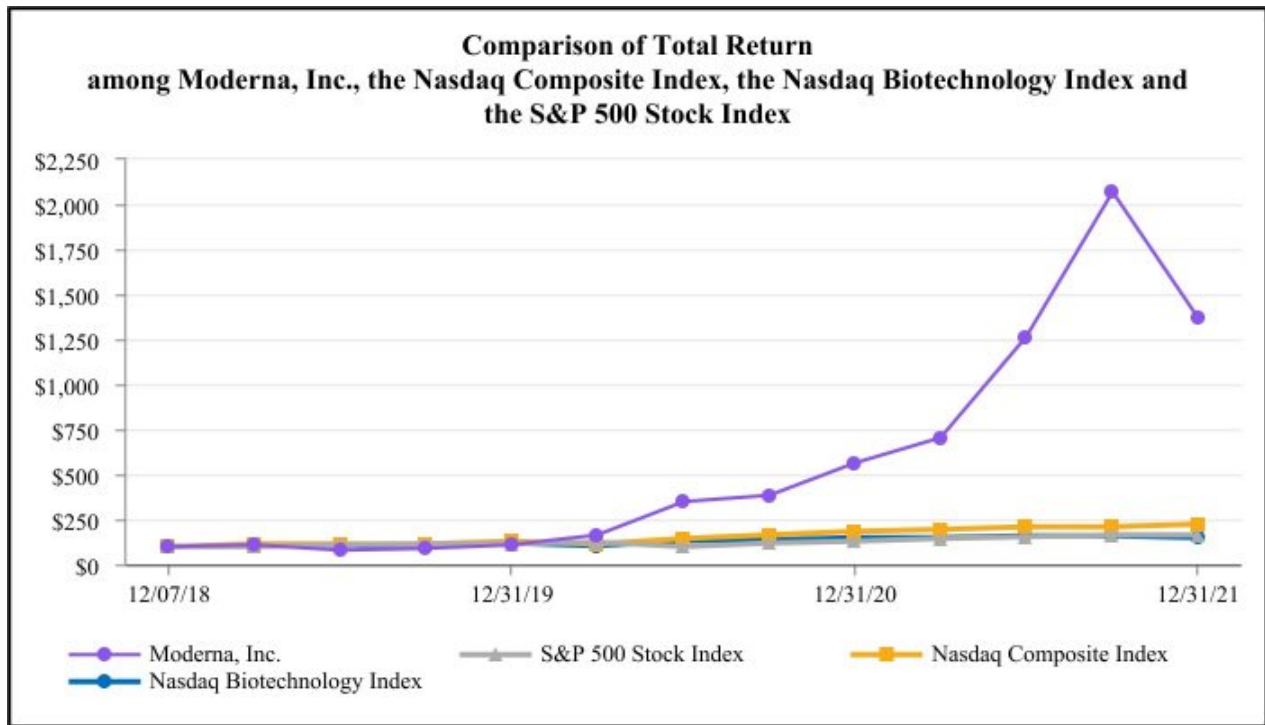
Our common stock began trading on the Nasdaq Global Select Market under the symbol “MRNA” on December 7, 2018. Prior to that time, there was no public market for our common stock.

Stock Performance Graph

The following performance graph shall not be deemed “soliciting material” or to be “filed” with the SEC for purposes of the Exchange Act or otherwise subject to the liabilities under that section, and shall not be deemed to be incorporated by reference into any filing of Moderna, Inc. under the Securities Act or the Exchange Act.

The following graph shows a comparison from December 7, 2018, the date on which our common stock first began trading on the Nasdaq Global Select Market, through December 31, 2021 of the cumulative total return for our common stock, the Nasdaq Composite Total Return Index and the Nasdaq Biotechnology Index, each of which assumes an initial investment of \$100 and reinvestment of all dividends. Such returns are based on historical results and are not intended to suggest future performance. In 2021, we became part of the Standard & Poor’s 500 Stock Index (the “S&P 500”). As a result, this year we are including the cumulative total return of that index in addition to the broad equity market indices that we included in our Annual Report on Form-10-K for the year ended December 31, 2020.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.



Stockholders

We had approximately 85 stockholders of record as of February 18, 2022. Because many of our outstanding shares are held in accounts with brokers and other institutions, the number of beneficial owners is significantly greater than the number of record holders. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

We have never declared or paid cash dividends on our common stock and do not expect to pay dividends on our common stock for the foreseeable future.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans in Item 12 of Part III of this Annual Report on Form 10-K is incorporated herein by reference. Any future determination to pay dividends will be made at the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects, then applicable contractual restrictions and any other factors deemed relevant by our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

The following table provides information with respect to the shares of common stock repurchased by us during the three months ended December 31, 2021:

Period	Total Number of Shares Purchased	Average Price Paid per Share ⁽¹⁾	Total Number of Shares Purchased as Part of Publicly Announced Program	Approximate Dollar Value of Shares that May Yet Be Purchased Under the Program
October 1 - October 31, 2021	189,212	\$ 317.10	189,212	\$ 940,000,261
November 1 - November 30, 2021	2,249,198	\$ 240.08	2,438,410	\$ 400,003,774
December 1 - December 31, 2021	1,049,732	\$ 245.06	3,488,142	\$ 142,751,231
Total	3,488,142			

⁽¹⁾ Average price paid per share includes related expenses.

On August 2, 2021, our Board of Directors authorized a Share Repurchase Program (2021 Repurchase Program) of our common stock, with an expiration date no later than August 2, 2023. Pursuant to the 2021 Repurchase Program, we may repurchase up to \$1.0 billion of our outstanding common stock. Since inception of the 2021 Repurchase Program through December 31, 2021, we repurchased a total of 3.5 million shares of our common stock for an aggregate purchase price of \$857 million. Subsequent to December 31, 2021, the remaining amounts authorized under the 2021 Repurchase Program have been fully utilized.

Item 6. [Reserved]

Item 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes and other financial information appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in "Part I, Item 1A - Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines to improve the lives of patients. mRNA medicines are designed to direct the body's cells to produce intracellular, membrane, or secreted proteins that have a therapeutic or preventive benefit with the potential to address a broad spectrum of diseases. Our platform builds on continuous advances in basic and applied mRNA science, delivery technology and manufacturing, providing us the capability to pursue in parallel a robust pipeline of new development candidates. We are developing therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases, autoimmune diseases and cardiovascular diseases, independently and with our strategic collaborators. In January 2022, the U.S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for our COVID-19 vaccine, Spikevax, for individuals 18 years of age and older in the United States. Spikevax is our first product to achieve licensure in the United States, and it has been authorized for use or approved by regulators in more than 70 countries.

Within our platform, we develop technologies that enable the development of mRNA medicines for diverse applications. When we identify technologies that we believe could enable a new group of potential mRNA medicines with shared product features, we call that group a "modality." While the programs within a modality may target diverse diseases, they share similar mRNA technologies, delivery technologies, and manufacturing processes to achieve shared product features. The programs within a modality will also generally share similar pharmacology profiles, including the desired dose response, the expected dosing regimen, the target tissue for protein expression, safety and tolerability goals, and pharmaceutical properties. Programs within a modality often have correlated technology risk, but because they pursue diverse diseases they often have uncorrelated biology risk. We have created seven modalities to date:

- prophylactic vaccines;
- systemic secreted and cell surface therapeutics;
- cancer vaccines;
- intratumoral immuno-oncology;
- localized regenerative therapeutics;
- systemic intracellular therapeutics; and
- inhaled pulmonary therapeutics.

We have designated our prophylactic vaccines and systemic secreted and cell surface therapeutics modalities as our "core modalities." In these core modalities, our strategy is to invest in additional development candidates using our accumulated innovations in technology, our process insights and our preclinical and clinical experience. Our exploratory modalities continue to be a critical part of advancing our strategy to maximize the application of our potential mRNA medicines.

Since our founding in 2010, we have transformed from a research-stage company advancing programs in the field of mRNA to a commercial enterprise with a diverse clinical portfolio of vaccines and therapeutics across seven modalities, a broad intellectual property portfolio in areas including mRNA and lipid nanoparticle formulation, and an integrated manufacturing plant that allows for rapid clinical and commercial production at scale. We have established relationships with a broad range of domestic and overseas government and commercial collaborators, which has allowed for the pursuit of both groundbreaking science and rapid scaling of our manufacturing capabilities. Most recently, our capabilities have come together to allow the authorization and approval of one of the earliest and most-effective vaccines against the COVID-19 pandemic.

2021 Business Highlights

Moderna COVID-19 Vaccine

On December 18, 2020, we received an Emergency Use Authorization (EUA) from the FDA for the emergency use of the Moderna COVID-19 Vaccine (also referred to as mRNA-1273 and marketed under the brand name Spikevax) in individuals 18 years of age or

older. Subsequently, we have also received authorization for our COVID-19 vaccine from health agencies in more than 70 countries and from the World Health Organization (WHO). Additional authorizations are currently under review in other countries. In addition, we have received authorization for our COVID-19 vaccine for use in adolescents in the European Union, the United Kingdom, Australia, Canada, Switzerland and other countries, and have pending applications for authorization to administer the vaccine to adolescents with regulatory agencies in the United States and other countries. In January 2022, we received full FDA approval for Spikevax to prevent COVID-19 in individuals 18 years of age and older in the United States.

A booster dose of our COVID-19 vaccine at the 50 µg dose level is authorized for use under an EUA for adults 18 years and older. A third dose of our COVID-19 vaccine at the 100 µg dose level is authorized for use under an EUA in immunocompromised individuals 18 years of age or older in the United States who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. The European Medicines Agency (EMA) has also authorized a third dose of the Moderna COVID-19 vaccine given at least 28 days after the second dose to severely immunocompromised individuals 12 years of age or older, as well as the administration of 50 µg booster doses for individuals 18 years of age and older.

Manufacturing Scaling

In 2021, we rapidly scaled our manufacturing capabilities for our COVID-19 vaccine. By June, we had delivered 200 million doses of the Moderna COVID-19 Vaccine to the U.S. government. By end of September, we and our partners ramped up our capacity worldwide and supplied more than 500 million doses of our COVID-19 vaccine globally. We took measures to scale capacity at a significant pace, including the expansion of our Moderna Technology Center (MTC) in Norwood, Massachusetts. By the end of 2021, we had shipped approximately 800 million doses of our COVID-19 vaccine worldwide.

In April 2021, we announced new funding commitments to increase supply at our owned and partnered manufacturing facilities. We expect these investments will allow for a doubling of drug substance manufacturing at Lonza's Switzerland-based facility, a more than doubling of formulation, fill and finish and drug substance manufacturing at Rovi's Spain-based facility, as well as a 50 percent increase of drug substance at Moderna's facilities in the U.S. When completed, the investments are also expected to result in an increase in safety stock of raw materials and finished product used to deliver committed volumes.

Access Expansion

We recognize that vaccine availability continues to be a challenge in many parts of the world, and we remain focused on ensuring that low-income countries have access to our vaccine. In April, we announced additional investments to increase global supply of our COVID-19 vaccine and in May we announced an agreement with Gavi, the Vaccine Alliance to supply up to 500 million doses of our vaccine at our lowest tiered price, in line with our global access commitments. This agreement has subsequently been revised to provide up to 650 million doses to be delivered across 2021 and 2022.

Additionally, in October, we announced that Moderna will build a state-of-the-art mRNA facility in Africa with the goal of producing up to 500 million doses of vaccines each year at the 50 µg dose level. We also announced the first step in our long-term partnership with the African Union with a Memorandum of Understanding to supply up to 110 million doses of our COVID-19 vaccine to address the needs of low-income countries in Africa. In January 2022, African Union informed us that it will not exercise its option for 60 million doses in the second quarter of 2022, due to its expectation that existing supplies will be sufficient to meet its vaccination targets.

Program Development

Throughout the year, we continued to build a diverse clinical portfolio of vaccines and therapeutics across our seven modalities. Our longstanding approach to portfolio development, pursuing programs that have shared technology or biology, has helped us reduce risk as our pipeline has grown to 40 programs in development, including 23 in clinical studies as of December 31, 2021.

Beyond our COVID-19 vaccine, in 2021 we launched the second pivotal trial in our company's history with CMVictory, a Phase 3 study of our vaccine to prevent congenital cytomegalovirus (CMV), which is the number one cause of birth defects in the U.S. This milestone takes us one step closer to potentially bringing another important vaccine to millions of people.

We are making other significant advances across our programs. Our seasonal influenza vaccine showed positive interim Phase 1 data, and our respiratory syncytial virus (RSV) vaccine moved to a Phase 2/3 trial of 34,000 participants in the fourth quarter of 2022. In oncology, our Personalized Cancer Vaccine Phase 2 trial is now fully enrolled, and we expect a readout as early as the fourth quarter of 2022. We also saw early positive data from the Phase 2 study of our mRNA VEGF-A therapeutic with AstraZeneca moving it to the next stage of clinical development.

Financial Highlights

We have entered into supply agreements with the U.S. Government, other international governments, Gavi (on behalf of the COVAX Facility), and the African Union for the supply of our COVID-19 vaccine. The agreements are generally subject to receipt of authorization or approval for the use and distribution of the vaccine from the relevant regulatory authority in each jurisdiction. Under these agreements, we are entitled to upfront deposits for our COVID-19 vaccine supply, which is initially recorded as deferred revenue. As of December 31, 2021, we had approximately \$6.7 billion in deferred revenue in connection with the supply agreements with the U.S. Government and other customers, which will be recognized as revenue when revenue recognition criteria have been met. For the year ended December 31, 2021, we delivered approximately 332 million doses of our COVID-19 vaccine to the U.S. Government and approximately 475 million doses to other governments, and we recognized \$17.7 billion in product sales.

As of December 31, 2021, we had cash, cash equivalents and investments of approximately \$17.6 billion. We are using this capital to fund operations and investing activities for technology creation, drug discovery and clinical development programs, infrastructure and capabilities to enable our research and early development activities (which includes our MTC), our digital infrastructure, creation of our portfolio of intellectual property, acquisition of key raw materials and supplies to support our commercial production quantities, development of a commercial team, expansion into global markets, funding our strategic collaborations and administrative support. We also use this capital to fund our Share Repurchase Program, designed to return value to our stockholders and minimize dilution from stock issuances.

Other Business Updates

In May 2021, we announced an expansion of our MTC. The MTC has been core to our long-term strategy and has enabled us to provide the scale and flexibility to support the development of our mRNA medicines and vaccines, including our COVID-19 vaccine. This investment will more than double the space at the MTC to approximately 650,000 square feet and allow us to continue to optimize our mRNA products as we explore new pharmaceutical delivery forms such as prefilled syringes and lyophilized products.

We are also investing in a new Moderna Science Center (MSC) in Cambridge, Massachusetts, to create a purpose-built space to support our next chapter of discovery and serve as our principal executive offices. The MSC will integrate digital-first scientific research and development labs along with space for innovation and co-creation with our people and our partners around the world. As part of our ongoing commitment to sustainability, the high-performance building is designed to be the most sustainable commercial lab building in Cambridge.

In addition to our owned facilities in the U.S., we have expanded our footprint across the globe, with active subsidiaries in more than 12 countries, including the U.S., Canada, many European countries and the Asia Pacific region. As Moderna expands internationally, we also announced in 2021 preliminary agreements with the governments of Canada and Australia to bring state-of-the-art mRNA manufacturing facilities to those countries to provide direct access to rapid pandemic response capabilities as well as domestically manufactured mRNA vaccines against other diseases.

Financial Operations Overview**Revenue**

The following table summarizes revenue for the periods presented (in millions):

	Years Ended December 31,		
	2021	2020	2019
Revenue:			
Product sales	\$ 17,675	\$ 200	\$ —
Grant revenue	735	529	12
Collaboration revenue	61	74	48
Total revenue	<u>\$ 18,471</u>	<u>\$ 803</u>	<u>\$ 60</u>

We began to record product sales for our COVID-19 vaccine subsequent to its authorization for emergency use by the FDA and Health Canada in December 2020. For the years ended December 31, 2021 and 2020, we recognized \$17.7 billion and \$200 million, respectively, of product sales from sales of our COVID-19 vaccine.

Other than product sales, our revenue in 2021 and 2020 was derived from government-sponsored and private organizations including BARDA, DARPA and the Bill & Melinda Gates Foundation and from strategic alliances with AstraZeneca, Merck and Vertex to discover, develop, and commercialize potential mRNA medicines.

The following table summarizes grant revenue for the periods presented (in millions):

	Years Ended December 31,		
	2021	2020	2019
BARDA	\$ 713	\$ 522	\$ 8
Other grant revenue	22	7	4
Total grant revenue	\$ 735	\$ 529	\$ 12

The following table summarizes collaboration revenue for the periods presented (in millions):

	Years Ended December 31,		
	2021	2020	2019
Collaboration revenue:			
AstraZeneca	\$ 7	\$ 33	\$ 5
Merck	23	26	37
Vertex	26	15	6
Other	5	—	—
Total collaboration revenue	\$ 61	\$ 74	\$ 48

As of December 31, 2021, we had signed supply agreements of approximately \$20.6 billion for the future supply of our COVID-19 vaccine to be delivered in 2022 and 2023 and had deferred revenue of \$6.7 billion associated with customer deposits received or billable under these agreements. Additional supply agreements have been agreed upon since December 31, 2021, and others are under discussion for 2022 and 2023 deliveries. We believe that the SARS-CoV-2 virus will evolve to an endemic phase in 2022 and as a result, we expect our product sales to be larger in the second half of 2022 than in the first half.

In addition, we expect to continue to receive funding from our contract with BARDA. As of December 31, 2021, the remaining available funding, net of revenue earned was \$189 million under the BARDA contract. To the extent that existing or potential future products generate revenue, our revenue may vary due to many uncertainties in future product demand, the development of our mRNA medicines and other factors.

Cost of sales

Cost of sales includes raw materials, personnel and facility and other costs associated with manufacturing our commercial product. These costs include production materials, production costs at our manufacturing facilities, third-party manufacturing costs, and final formulation and packaging costs. Cost of sales also includes shipping costs, royalties payable to third parties based on sales of our products, and charges for inventory valuation reserves.

Research and development expenses

The nature of our business and primary focus of our activities generate a significant amount of research and development costs.

Research and development expenses represent costs incurred by us for the following:

- cost to develop our platform;
- discovery efforts leading to development candidates;
- preclinical, nonclinical, and clinical development costs for our programs;
- cost to develop our manufacturing technology and infrastructure; and
- digital infrastructure costs related to our drug discovery efforts and clinical trials.

The costs above comprise the following categories:

- personnel-related expenses, including salaries, benefits, and stock-based compensation expense;
- expenses incurred under agreements with third parties, such as consultants, investigative sites, contract research organizations, or CROs, that conduct our preclinical studies and clinical trials, and in-licensing arrangements;

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- expenses associated with developing manufacturing capabilities and acquiring materials for preclinical studies, clinical trials and pre-launch inventory, including both internal manufacturing and third-party contract manufacturing organizations, or CMOs;
- expenses incurred for the procurement of materials, laboratory supplies, and non-capital equipment used in the research and development process; and
- facilities, depreciation, and amortization, and other direct and allocated expenses incurred as a result of research and development activities.

We use our employee and infrastructure resources for the advancement of our platform, and for discovering and developing programs. Due to the number of ongoing programs and our ability to use resources across several projects, indirect or shared operating costs incurred for our research and development programs are generally not recorded or maintained on a program- or modality-specific basis.

The following table reflects our research and development expenses, including direct program specific expenses summarized by modality and indirect or shared operating costs summarized under other research and development expenses during the years ended December 31, 2021, 2020, and 2019 (in millions):

	Years Ended December 31,		
	2021	2020	2019
Program expenses by modality:			
Prophylactic vaccines	\$ 1,099	\$ 707	\$ 48
Systemic secreted and cell surface therapeutics	3	2	11
Cancer vaccines	47	29	44
Intratumoral immuno-oncology	20	9	18
Localized regenerative therapeutics	—	—	3
Systemic intracellular therapeutics	26	21	33
Inhaled pulmonary therapeutics	1	—	—
Total program-specific expenses by modality ⁽¹⁾	\$ 1,196	\$ 768	\$ 157
Other research and development expenses:			
Discovery programs	\$ 85	\$ 56	\$ 56
Platform research	125	93	91
Technical development and unallocated manufacturing expenses	275	279	85
Shared discovery and development expenses	242	118	59
Stock-based compensation	68	56	48
Total research and development expenses	\$ 1,991	\$ 1,370	\$ 496

⁽¹⁾ Includes a total of 37 development candidates at December 31, 2021 and 21 development candidates at each of December 31, 2020 and 2019. Program-specific expenses include external costs and allocated manufacturing costs of pre-launch inventory, mRNA supply and consumables, and are reflected as of the beginning of the period in which the program was internally advanced to development or removed if development was ceased.

A “modality” refers to a group of programs with common product features and the associated combination of enabling mRNA technologies, delivery technologies, and manufacturing processes. The program-specific expenses by modality summarized in the table above include expenses we directly attribute to our programs, which consist primarily of external costs, such as fees paid to outside consultants, central laboratories, investigative sites, and CROs in connection with our preclinical studies and clinical trials, CMOs, and allocated manufacturing costs of pre-launch inventory, mRNA supply and consumables. Costs to acquire and manufacture pre-launch inventory, mRNA supply for preclinical studies and clinical trials are recognized and included in unallocated manufacturing expenses when incurred, and subsequently allocated to program-specific manufacturing costs after completion of the program-specific production. The timing of allocating manufacturing costs to the specific program varies depending on the program development and production schedule. We generally do not allocate personnel-related costs, including stock-based compensation, costs associated with our general platform research, technical development, and other shared costs on a program-specific basis. These costs were therefore excluded from the summary of program-specific expenses by modality.

Discovery program expenses are costs associated with research activities for our programs in the preclinical discovery stage, and primarily consist of external costs for CROs and lab services, and allocated manufacturing cost of preclinical mRNA supply and consumables.

Platform research expenses are mainly costs to develop technical advances in mRNA science, delivery science, and manufacturing process design. These costs include personnel-related costs, computer equipment, facilities, preclinical mRNA supply and consumables, and other administrative costs to support our platform research. Technology development and unallocated manufacturing expenses are primarily related to non-program-specific manufacturing process development and manufacturing costs.

Shared discovery and development expenses are research and development costs such as personnel-related costs and other costs, which are not otherwise included in development programs, discovery programs, platform research, technical development and unallocated manufacturing expenses, stock-based compensation, and other expenses.

The largest component of our total operating expenses has historically been our investment in research and development activities, including development of our platform, mRNA technologies, and manufacturing technologies. We expense research and development costs as incurred and cannot reasonably estimate the nature, timing, and estimated costs required to complete the development of the development candidates and investigational medicines we are currently developing or may develop in the future. There are numerous risks and uncertainties associated with the research and development of such development candidates and investigational medicines, including, but not limited to:

- scope, progress, and expense of developing ongoing and future development candidates and investigational medicines;
- entry in and completion of related preclinical studies;
- enrollment in and completion of subsequent clinical trials;
- safety and efficacy of investigational medicines resulting from these clinical trials;
- changes in laws or regulations relevant to the investigational medicines in development;
- receipt of the required regulatory approvals; and
- commercialization, including establishing manufacturing and marketing capabilities.

As we continue to pursue our indication expansion of mRNA-1273 during the current pandemic, and continue to develop variant-specific COVID-19 vaccine candidates and our next-generation COVID-19 vaccine candidate (mRNA-1283), we expect to continue to incur significant additional expenses. At this time, the magnitude of these potential expenditures is not known. In connection with the BARDA agreement to accelerate development of mRNA-1273, grant revenue and expenses within the committed funding scope are expected to continue in 2022. BARDA's funding is expected to offset those expenses that are covered under the BARDA agreement, subject to our obtaining reimbursement from BARDA. As of December 31, 2021, the remaining available funding from BARDA, net of revenue earned was \$189 million. Please refer to Note 4 to our consolidated financial statements.

Changes in expectations or outcomes of any of the known or unknown risks and uncertainties may materially impact our expected research and development expenditures. Continued research and development is central to the ongoing activities of our business. Investigational medicines in later stages of clinical development, such as our CMV vaccine (mRNA-1647) and our COVID-19 vaccine, generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect our research and development costs to continue to increase for the foreseeable future as our investigational medicines progress through the development phases and as we identify and develop additional programs. There are numerous factors associated with the successful commercialization of any of our investigational medicines, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time due to the early stage of development of our investigational medicines. Moreover, future commercial and regulatory factors beyond our control will impact our clinical development programs and plans.

Selling, general and administrative expenses

We started to incur sales and marketing expenses in the fourth quarter of 2020 to prepare for commercial operations in connection with the sale of our COVID-19 vaccine, and these expenses increased throughout the course of 2021. Selling, general and administrative expenses consist primarily of personnel-related costs, including stock-based compensation, for executives, finance, legal, human resources, business development and other administrative and operational functions, professional fees, accounting and legal services, information technology and facility-related costs, and expenses associated with obtaining and maintaining intellectual property, or IP. These costs relate to the operation of the business, unrelated to the research and development function, or any individual program.

We anticipate selling, general and administrative expenses will increase as we continue to expand the number of programs in development and prepare for the establishment of commercial activities both within and outside the United States. We have already incurred additional expenses related to building out a regulatory, sales and marketing team to support the sale, marketing and distribution of our COVID-19 vaccine and the expansion of our footprint across the globe, with active subsidiaries in more than 12 countries. If we obtain regulatory approval for additional investigational medicines, and do not enter into one or more third-party

commercialization collaboration and manufacturing arrangements, we will incur significant additional expenses related to building out these functions.

We have a broad IP portfolio covering our development and commercialization of mRNA vaccine and therapeutic programs, including those related to mRNA design, formulation, and manufacturing platform technologies. We regularly file patent applications to protect innovations arising from our research and development. We also hold trademarks and trademark applications in the United States and foreign jurisdictions. Costs to secure and defend our IP are expensed as incurred, and are classified as selling, general and administrative expenses.

Interest income

Interest income consists of interest generated from our investments in cash and cash equivalents, money market funds, and high-quality fixed income securities.

Other expense, net

Other expense, net consists of interest expense, gains (losses) from the sale of investments in marketable securities, and other income and expense unrelated to our core operations. Interest expense is primarily derived from our finance leases related to our Moderna Technology Center and certain contract manufacturing service agreements.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make judgments and estimates that affect the reported amounts of assets, liabilities, revenues, and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events, and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. On an ongoing basis, we evaluate our judgments and estimates in light of changes in circumstances, facts, and experience. The effects of material revisions in estimates, if any, are reflected in the consolidated financial statements prospectively from the date of change in estimates.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies used in the preparation of our consolidated financial statements require the most significant judgments and estimates.

Income taxes

We account for income taxes based on an asset and liability approach. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. We determine our deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided, if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. We consider future taxable income, ongoing tax planning strategies and our historical financial performance in assessing the need for a valuation allowance. If we expect to realize deferred tax assets for which we have previously recorded a valuation allowance, we will reduce the valuation allowance in the period in which such determination is first made. As of December 31, 2021, we maintained a valuation allowance against a portion of the state deferred tax assets based on management's evaluation of all available evidence.

We are subject to income tax audits and adjustments by tax authorities. The nature of uncertain tax positions is subject to significant judgment by management and subject to change, which may be substantial. We develop our assessment of uncertain tax positions and as additional information becomes available, estimates are revised and refined. We record reserves for potential tax payments to various tax authorities related to uncertain tax positions. These reserves are based on a determination of whether and how much of a tax benefit taken by us in our tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit. Differences between estimates and final settlement may occur resulting in additional tax expense.

Recently issued accounting pronouncements

We have reviewed all recently issued standards and have determined that such standards will not have a material impact on our financial statements or do not otherwise apply to our operations.

Results of operations

A discussion regarding our results of operations for the year ended December 31, 2021 compared to 2020 is presented below. A discussion regarding our results of operations for the year ended December 31, 2020 compared to 2019 can be found under Part II -Item 7 of our Annual Report on Form 10-K for the year ended December 31, 2020, which was filed with the Securities and Exchange Commission (SEC) on February 26, 2021.

The following tables summarize our consolidated statements of operations for the periods presented (in millions):

	Years Ended December 31,		Change 2021 vs. 2020	
	2021	2020	Change	%
Revenue:				
Product sales	\$ 17,675	\$ 200	\$ 17,475	8,738 %
Grant revenue	735	529	206	39 %
Collaboration revenue	61	74	(13)	(18)%
Total revenue	18,471	803	17,668	2,200 %
Operating Expenses:				
Cost of sales	2,617	8	2,609	32,613 %
Research and development	1,991	1,370	621	45 %
Selling, general and administrative	567	188	379	202 %
Total operating expenses	5,175	1,566	3,609	230 %
Income (loss) from operations	13,296	(763)	14,059	1,843 %
Interest income	18	25	(7)	(28)%
Other expense, net	(29)	(6)	(23)	383 %
Income (loss) before income taxes	13,285	(744)	14,029	1,886 %
Provision for income taxes	1,083	3	1,080	36,000 %
Net income (loss)	\$ 12,202	\$ (747)	\$ 12,949	1,733 %

	Years Ended December 31,		Change 2020 vs. 2019	
	2020	2019	Change	%
Revenue:				
Product sales	\$ 200	\$ —	\$ 200	100 %
Grant revenue	\$ 529	\$ 12	\$ 517	4,308 %
Collaboration revenue	74	48	26	54 %
Total revenue	803	60	743	1,238 %
Operating Expenses:				
Cost of sales	8	—	8	100 %
Research and development	1,370	496	874	176 %
Selling, general and administrative	188	110	78	71 %
Total operating expenses	1,566	606	960	158 %
Loss from operations	(763)	(546)	(217)	40 %
Interest income	25	39	(14)	(36)%
Other expense, net	(6)	(8)	2	(25)%
Loss before income taxes	(744)	(515)	(229)	44 %
Provision for (benefit from) income taxes	3	(1)	4	(400)%
Net loss	\$ (747)	\$ (514)	\$ (233)	45 %

Revenue

Total revenue increased by \$17.7 billion in 2021, primarily due to increases in product sales. Product sales increased by \$17.5 billion in 2021 from sales of our COVID-19 vaccine to domestic and international government customers and international purchasing organizations, such as Gavi (on behalf of the COVAX Facility) and the African Union, subsequent to the authorization by the FDA and Health Canada for emergency use in December 2020. Grant revenue increased by \$206 million, or 39%, in 2021, mainly due to an increase in grant revenue from BARDA related to our COVID-19 vaccine development in 2021.

Operating expenses

Cost of sales

We began capitalizing our COVID-19 vaccine inventory costs in December 2020, in connection with an Emergency Use Authorization from the FDA and an Interim Order from Health Canada for use of our COVID-19 vaccine, and based upon our expectation that these costs would be recoverable through commercialization of mRNA-1273. Prior to the capitalization of our COVID-19 vaccine inventory costs, costs related to our pre-launch inventory were recorded as research and development expenses in the period incurred. We expensed \$242 million of pre-launch inventory costs in 2020.

Our cost of sales was \$2.6 billion, or 15% of our product sales, in 2021, including third-party royalties of \$641 million. A portion of the inventory costs associated with our product sales for the year ended 2021 was expensed previously. If inventory sold for the year ended 2021 was valued at cost, including what was expensed as pre-launch inventory, our cost of sales for the period would have been \$2.8 billion, or 16% of our product sales. We utilized all of our pre-launch inventory during 2021. We expect that our cost of sales as a percentage of product sales will increase in 2022 due to higher manufacturing costs and lower average selling price per dose, driven by the expected increase in deliveries to low income countries.

Research and development expenses

Research and development expenses increased by \$621 million, or 45%, in 2021. The increase was primarily attributable to an increase in clinical trial expenses of \$721 million, an increase in personnel-related costs of \$79 million, and an increase in consulting and outside services of \$59 million, partially offset by a decrease in manufacturing expenses of \$251 million, attributable to pre-launch inventory expensed in 2020 prior to FDA authorization. The increase in 2021 was largely attributable to the continued clinical development of mRNA-1273. The increase in personnel-related costs was primarily driven by an increase in the number of employees supporting our mRNA-1273 development activities as well as other research and development programs.

We expect that research and development expenses will increase in 2022 as we continue to progress our indication expansion of mRNA-1273, and continue to develop our pipeline and advance our product candidates into later-stage development. In addition, we also expect to incur significant costs related to the development of variant-specific COVID-19 candidates and our next-generation COVID-19 vaccine candidate (mRNA-1283).

Selling, general and administrative expenses

Selling, general and administrative expenses increased by \$379 million, or 202%, in 2021. The increase was mainly due to an increase in consulting and outside services of \$97 million, an increase in personnel-related costs of \$73 million, an increase in marketing expense of \$67 million, an increase in distributor fees of \$64 million, and an increase in legal, licensing and insurance expenses of \$42 million. The increases in personnel-related costs and consulting and outside services were primarily attributable to mRNA-1273 commercialization-related activities and increased headcount.

We expect that selling, general and administrative expenses will increase in 2022, as we continue to build out our global commercial, regulatory, sales and marketing infrastructure to support the commercialization of our COVID-19 vaccine, and continue to expand the number of programs and our business operations.

Interest income

Interest income generated from our investments in marketable securities decreased by \$7 million, or 28%, in 2021, mainly attributable to an overall lower interest rate.

Other expense, net

The following table summarizes other expense, net for the periods presented (in millions):

	Years Ended December 31,		Change 2021 vs. 2020	
	2021	2020	Change	%
Gain on investments	\$ 1	\$ 1	\$ —	— %
Interest expense	(18)	(10)	(8)	80 %
Other (expense) income, net	(12)	3	(15)	(500)%
Total other expense, net	<u>\$ (29)</u>	<u>\$ (6)</u>	<u>\$ (23)</u>	383 %

Total other expense, net increased by \$23 million, or 383%, in 2021. The increase was primarily due to losses related to remeasurements and our balance sheet hedging activities, partially offset by gains on foreign currency transactions. Our interest expense is primarily related to our finance leases. The increase in interest expense was driven by new finance leases that commenced in 2021. Please refer to Note 11 to our consolidated financial statements.

Provision for income taxes

Provision for income taxes increased by \$1.1 billion in 2021, primarily due to an increase in pre-tax income. Our effective tax rate for the year ended December 31, 2021 was 8.1%, which included tax benefits related to the release of the valuation allowance on most of our deferred tax assets, foreign-derived intangible income deduction, and stock-based compensation. Provision for income taxes was immaterial for the year ended December 31, 2020. We expect that our effective tax rate will increase in 2022 as the valuation allowance against our deferred tax assets was mostly released in 2021.

Liquidity and capital resources

Prior to the commercialization of our COVID-19 vaccine, we have historically funded our operations primarily from the sale of equity instruments and from proceeds from certain strategic alliance arrangements and grant agreements. Starting in August 2020, we entered into supply agreements with the U.S. Government, other international governments, Gavi, and the African Union for the supply of our COVID-19 vaccine. Under these agreements, we are entitled to upfront deposits for our COVID-19 vaccine supply, which are initially recorded as deferred revenue and will be recognized as revenue when revenue recognition criteria have been met. As of December 31, 2021, we had \$6.7 billion in deferred revenue related to customer deposits received or billable. In addition, we expect to continue to receive funding from our contract with BARDA related to our mRNA-1273 program. As of December 31, 2021, the remaining available funding, net of revenue earned was \$189 million.

As of December 31, 2021, we had cash, cash equivalents and investments of \$17.6 billion. Cash, cash equivalents and investments are invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation. Investments, consisting primarily of government and corporate debt securities are stated at fair value. As of December 31, 2021, we had current and non-current investments of approximately \$3.9 billion and \$6.8 billion, respectively.

Effective January 1, 2022, research and development expenses are required to be capitalized and amortized for U.S. tax purposes. Unless modified or repealed, and based on current assumptions, the mandatory capitalization would increase our cash tax liabilities.

We continue to work toward the large-scale technical development, manufacturing scale-up in several countries and larger scale deployment of our COVID-19 vaccine. To support the scale-up, we have expended and will need to continue to expend significant resources and capital.

Cash flow

The following table summarizes the primary sources and uses of cash for the periods presented (in millions):

	Years Ended December 31,		
	2021	2020	2019
Net cash provided by (used in):			
Operating activities	\$ 13,620	\$ 2,027	\$ (459)
Investing activities	(8,523)	(1,672)	(15)
Financing activities	(873)	2,033	52
Net increase (decrease) in cash and cash equivalents	<u>\$ 4,224</u>	<u>\$ 2,388</u>	<u>\$ (422)</u>

Operating activities

We derive cash flows from operations primarily from cash collected from customer deposits related to our COVID-19 vaccine supply agreements as well as certain government-sponsored and private organizations and strategic alliances. Our cash flows from operating activities are significantly affected by our use of cash for operating expenses and working capital to support the business. Prior to 2020, we experienced negative cash flows from operating activities as we invested in our mRNA technologies, development pipeline, digital infrastructure, manufacturing technology, and infrastructure.

Net cash provided by operating activities in 2021 was \$13.6 billion and consisted of net income of \$12.2 billion and non-cash adjustments of \$110 million, plus a net change in assets and liabilities of \$1.3 billion. Non-cash items primarily included depreciation and amortization of \$232 million, stock-based compensation of \$142 million, deferred income taxes of \$318 million, and amortization of investment premiums and discounts of \$54 million. The net change in assets and liabilities was primarily due to an increase in deferred revenue of \$2.8 billion, an increase in accrued liabilities of \$989 million, an increase in income taxes payable of \$876 million, and an increase in accounts payable of \$204 million, partially offset by an increase in accounts receivable of \$1.8 billion, an increase in inventory of \$1.4 billion, and an increase in prepaid expenses and other assets of \$489 million.

Net cash provided by operating activities in 2020 was \$2.0 billion and consisted of net loss of \$747 million less non-cash adjustments of \$196 million, plus a net change in assets and liabilities of \$2.6 billion. Non-cash items primarily included stock-based compensation of \$93 million, leased assets expensed of \$62 million, depreciation and amortization of \$31 million, and amortization of investment premiums and discounts of \$10 million. The net change in assets and liabilities was primarily due to an increase in deferred revenue of \$3.8 billion, an increase in accrued liabilities of \$388 million, an increase in accounts payable of \$12 million, and an increase in operating lease liabilities of \$12 million, partially offset by an increase in accounts receivable of \$1.4 billion, an increase in prepaid expenses and other assets of \$241 million, an increase of inventory of \$47 million, and an increase in operating lease right-of-use assets of \$11 million.

Net cash used in operating activities in 2019 was \$459 million and consisted of net loss of \$514 million less non-cash adjustments of \$108 million, plus a net change in assets and liabilities of \$53 million. Non-cash items primarily included stock-based compensation of \$81 million, and depreciation and amortization of \$31 million. The net change in assets and liabilities was primarily due to a decrease in deferred revenue of \$44 million, and a decrease in accounts payable of \$24 million, partially offset by an increase in operating lease liabilities, non-current of \$13 million, and a decrease in prepaid expenses and other assets of \$10 million.

Investing activities

Our primary investing activities consist of purchases, sales, and maturities of our investments and capital expenditures for manufacturing, laboratory, computer equipment, and software.

Net cash used in investing activities in 2021 was \$8.5 billion, which included purchases of marketable securities of \$12.7 billion, purchases of property and equipment of \$284 million, and investment in convertible notes of \$30 million, partially offset by proceeds from sales of marketable securities of \$3.1 billion and proceeds from maturities of marketable securities of \$1.3 billion.

Net cash used in investing activities in 2020 was \$1.7 billion, which included purchases of marketable securities of \$3.0 billion and purchases of property and equipment of \$68 million, partially offset by proceeds from maturities of marketable securities of \$1.1 billion and proceeds from sales of marketable securities of \$215 million.

Net cash used in investing activities in 2019 was \$15 million, which included purchases of marketable securities of \$1.1 billion and purchases of property and equipment of \$32 million, partially offset by proceeds from maturities of marketable securities of \$993 million and proceeds from sales of marketable securities of \$169 million.

Financing activities

Net cash used in financing activities in 2021 was \$873 million, primarily from repurchases of common stock of \$857 million and changes in financing lease liabilities of \$140 million, partially offset by net proceeds from the issuance of common stock in connection with the exercise of stock options and employee stock purchases under our equity plans of \$124 million.

Net cash provided by financing activities in 2020 was \$2.0 billion, primarily from net proceeds from equity offerings of \$1.9 billion and net proceeds from the issuance of common stock in connection with the exercise of stock options and employee stock purchases under our equity plans of \$186 million.

Net cash provided by financing activities in 2019 was \$52 million, primarily from net proceeds from the issuance of common stock in connection with the exercise of stock options and employee stock purchases under our equity plans of \$51 million.

Operation and funding requirements

From our inception to the end of 2020, we incurred significant losses from operations due to our significant research and development expenses. We generated net income for the year ended 2021 in connection with product sales following the authorization of our first commercial product. We have retained earnings of \$10.0 billion as of December 31, 2021. We have significant future capital requirements including expected operating expenses to conduct research and development activities, operate our organization, meet capital expenditure needs, and fund our share repurchase program. We expect our expenses to increase in connection with our ongoing activities as we continue research and development of our development candidates and clinical activities for our investigational medicines. We also expect our expenses to increase associated with manufacturing costs, including our arrangements with our international supply and manufacturing partners. Our ongoing work on mRNA-1273, including development of any new generations of boosters and vaccines against variants of SARS-CoV-2, and buildout of global commercial, regulatory, sales and marketing infrastructure to support the commercialization of our COVID-19 vaccine will require significant cash outflows during 2022, most of which may not be reimbursed or otherwise paid for by our partners or collaborators. In addition, we have substantial facility, lease and purchase obligations. We have entered into certain collaboration agreements with third parties that include the funding of certain research and development activities and potential future milestone and royalty payments by us.

We believe that our cash, cash equivalents, and investments as of December 31, 2021, will be sufficient to enable us to fund our projected operations, capital expenditures and share repurchases through at least the next 12 months from the issuance of the financial statements included in this Annual Report on Form 10-K. We are subject to all the risks related to the development and commercialization of novel medicines, and we may encounter unforeseen expenses, difficulties, complications, delays, and other unknown factors including expenses related to the ongoing COVID-19 pandemic, which may adversely affect our business. Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect.

If we fail to sustain profitability on a continuing basis, we may be required to finance future cash needs through a combination of public or private equity offerings, structured financings and debt financings, government funding arrangements, potential future strategic alliances from which we receive upfront fees, milestone payments, and other forms of consideration, and marketing, manufacturing, distribution and licensing arrangements. If we are required to finance future cash needs, additional capital may not be available on reasonable terms, if at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back, or discontinue the development or commercialization of one or more of our investigational medicines, or slow down or cease work on one or more of our programs. If we raise additional funds through the issuance of additional equity or debt securities, it could result in dilution to our existing stockholders or increased fixed payment obligations, and any such securities may have rights senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise funds through strategic alliances or marketing, distribution, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs, or investigational medicines or grant licenses on terms that may not be favorable to us. Any of these events could significantly harm our business, financial condition, and prospects.

Contractual obligations and commitments

The following table summarizes our contractual obligations as of December 31, 2021 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods (in millions):

	Payments Due by Period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
Operating leases	\$ 191	\$ 54	\$ 54	\$ 32	\$ 51
Financing leases ⁽¹⁾	1,323	184	40	41	1,058
MSC lease ⁽²⁾	1,051	—	65	117	869
Purchase obligations ⁽³⁾	2,587	2,004	541	42	—
Total contractual cash obligations	\$ 5,152	\$ 2,242	\$ 700	\$ 232	\$ 1,978

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- (1) The amounts in the table include a total payment of \$637 million associated with our MTC leases for the optional lease extension periods. For accounting purpose, a lease term is the non-cancelable period of the lease and includes options to extend or terminate the lease when it is reasonably certain that an option will be exercised. Please refer to Note 11 to our consolidated financial statements.
 - (2) We entered into a lease agreement for approximately 462,000 square feet in Cambridge, Massachusetts (Moderna Science Center) and will undergo an approximately two-year building project. Following the building project, the lease term is 15 years, subject to our right to extend the lease for up to two additional seven-year terms. The rent will commence on the Initial Phase Commencement date defined in the lease agreement that is currently estimated to be in July 2023.
 - (3) The amounts represent non-cancelable fixed payment obligations related to purchases of raw materials, contract manufacturing services, clinical services and other goods or services in the normal course of business.

We have agreements with certain vendors for various services, including services related to clinical operations, and support and contract manufacturing, which we are not contractually able to terminate for convenience. Certain agreements provide for termination rights subject to termination fees or wind down costs. Under such agreements, we are contractually obligated to make certain payments to vendors, mainly to reimburse them for their unrecoverable outlays incurred prior to cancellation. The exact amounts of such obligations are dependent on the timing of termination, and the exact terms of the relevant agreement and cannot be reasonably estimated. At December 31, 2021, we had cancelable open purchase orders of \$2.4 billion in total under such agreements for our clinical operations and support and contract manufacturing. These amounts represent only our estimate of those items for which we had a contractual commitment to pay at December 31, 2021, assuming we would not cancel these agreements. The actual amounts we pay in the future to the vendors under such agreements may differ from the cancelable open purchase order amounts of \$2.4 billion.

In addition to the above obligations, we enter into a variety of agreements and financial commitments in the normal course of business. The terms generally allow us the option to cancel, reschedule, and adjust our requirements based on our business needs, prior to the delivery of goods or performance of services. It is not possible to predict the maximum potential amount of future payments under these agreements due to the conditional nature of our obligations and the unique facts and circumstances involved in each particular agreement.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Interest Rate Risk

As of December 31, 2021 and 2020, we had cash, cash equivalents, restricted cash, and investments in marketable securities of \$17.6 billion and \$5.2 billion, respectively. Our investment portfolio comprises money market funds and marketable debt securities (including U.S. Treasury securities, debt securities of U.S. government agencies and corporate entities, and commercial paper), which are classified as available-for-sale securities. Our primary investment objectives are the preservation of capital and the maintenance of liquidity, and our investment policy defines allowable investments based on quality of the institutions and financial instruments designed to minimize risk exposure. Our exposure to interest rate sensitivity is affected by changes in the general level of U.S. interest rates.

Our marketable securities are subject to interest rate risk and will fall in value if market interest rates increase. Due to the short-term maturities and low risk profiles of our investments, we do not anticipate a significant exposure to interest rate risk. If market interest rates were to increase immediately and uniformly by one percentage point from levels at December 31, 2021, the net fair value of our marketable securities would decrease by approximately \$146 million.

Foreign Currency Risk

Our revenue generating activities and operations have been primarily denominated in U.S. dollars. Our significant foreign currency revenue exposure for the year ended December 31, 2021 was the equivalent of \$5.9 billion in Euros. As we expand internationally our results of operations and cash flows become increasingly subject to fluctuations due to changes in foreign currency exchange rates. To help manage the exposure to foreign currency exchange rate fluctuations, we have implemented cash flow hedging and balance sheet hedging programs.

Cash Flow Hedging Activities

We hedge foreign currency product sales denominated in Euros, including the use of foreign exchange forward contracts or purchased options. We hedge our cash flow exposures to reduce the risk that our earnings and cash flows will be adversely affected by changes in exchange rates. These transactions are designated and qualify as cash flow hedges. Our foreign exchange contracts as of December 31, 2021, carried at fair value, had maturities of up to 9 months.

Balance Sheet Hedging Activities

We use foreign currency forward contracts to mitigate foreign currency exchange risk associated with foreign currency-denominated monetary assets and liabilities. These contracts reduce the impact of currency exchange rate movements on our assets and liabilities. As of December 31, 2021, our outstanding balance sheet hedging derivatives, carried at fair value, had maturities of less than three months.

We enter into these foreign exchange contracts to hedge our forecasted revenue and monetary assets and liabilities denominated in foreign currency in the normal course of business and accordingly, they are not speculative in nature. We believe the counterparties to our foreign currency forward contracts are creditworthy multinational commercial banks. While we believe the risk of counterparty nonperformance is not material, a sustained decline in the financial stability of financial institutions as a result of disruption in the financial markets could affect our ability to secure creditworthy counterparties for our foreign currency hedging programs.

Notwithstanding our efforts to mitigate some foreign currency exchange risks, there can be no assurance that our hedging activities will adequately protect us against the risks associated with foreign currency fluctuations. As of December 31, 2021, a hypothetical adverse movement of 10 percent in foreign currency exchange rates compared to the U.S. dollars across all maturities would have resulted in potential declines in the fair value on our foreign currency forward contracts used in cash flow hedging of approximately \$54 million. As of December 31, 2021, a hypothetical adverse movement of 10 percent in foreign currency exchange rates compared to the U.S. dollars across all maturities would have resulted in potential declines in the fair value on our foreign currency forward contracts used in balance sheet hedging of approximately \$115 million. We expect that any increase or decrease in the fair value of the portfolio would be substantially offset by increases or decreases in the underlying exposures being hedged.

Item 8. Financial Statements and Supplementary Data

**MODERNA, INC.
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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Moderna, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Moderna, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive income (loss), stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 25, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Product Sales Revenue Recognition

Description of the Matter

As discussed in Note 2 to the consolidated financial statements, the Company has entered into supply agreements with the U.S. Government, other international governments, Gavi (on behalf of the COVAX facility), and the African Union. Under the supply agreements, the Company is entitled to upfront deposits for COVID-19 vaccine supply, which are initially recorded as deferred revenue. Revenue is recognized pursuant to Accounting Standards Codification Topic 606, Revenue from Contracts with Customers, based on the fixed price per dose when control of the product has transferred and customer acceptance has occurred, unless such acceptance provisions are deemed perfunctory. The Company must evaluate the contractual terms and conditions in its supply agreements to determine the timing of revenue recognition. For the year ended December 31, 2021, product sales revenue totaled \$17.7 billion and related deferred revenue totaled \$6.7 billion.

How We Addressed the Matter in Our Audit

Auditing the Company's revenue recognition was especially challenging due to the volume of executed supply agreements, the varying contractual terms within the agreements, and because the amounts are material to the consolidated financial statements and related disclosures.

We obtained an understanding, evaluated the design, and tested the operating effectiveness of the Company's internal controls over the recognition of revenue related to product sales. This included testing controls over the Company's process to evaluate the contractual terms of the supply agreements and determine the appropriate revenue recognition. We also tested the Company's controls over evaluating transfer of control and customer acceptance, as applicable, and controls over the Company's IT systems that are important to the initiation, processing and recording of revenue transactions.

To test the recognition of revenue associated with supply agreements, our audit procedures included, among others, evaluating the contractual terms of supply agreements, testing the transfer of control, and assessing the timing of revenue recognition. For example, we performed procedures to test the completeness and accuracy of the underlying data in the Company's revenue and deferred revenue calculations, including testing the mathematical accuracy of the Company's calculations, and testing the accuracy of revenue recognized by tracing key terms to the supply agreements and agreeing a sample of revenue transactions to supporting documentation, including evidence of control transfer. We also assessed the appropriateness of the related disclosures in the consolidated financial statements.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.

Boston, Massachusetts

February 25, 2022

MODERNA, INC.
CONSOLIDATED BALANCE SHEETS
(In millions, except per share data)

	December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	\$ 6,848	\$ 2,624
Investments	3,879	1,984
Accounts receivable	3,175	1,391
Inventory	1,441	47
Prepaid expenses and other current assets	728	252
Total current assets	16,071	6,298
Investments, non-current	6,843	639
Property and equipment, net	1,241	297
Right-of-use assets, operating leases	142	90
Restricted cash, non-current	12	11
Deferred tax assets	326	—
Other non-current assets	34	2
Total assets	<u>\$ 24,669</u>	<u>\$ 7,337</u>
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	\$ 302	\$ 18
Accrued liabilities	1,472	470
Deferred revenue	6,253	3,867
Income taxes payable	876	—
Other current liabilities	225	34
Total current liabilities	9,128	4,389
Deferred revenue, non-current	615	177
Operating lease liabilities, non-current	106	97
Financing lease liabilities, non-current	599	110
Other non-current liabilities	76	3
Total liabilities	10,524	4,776
Commitments and contingencies (Note 12)		
Stockholders' equity:		
Preferred stock, \$0.0001; 162 shares authorized as of December 31, 2021 and 2020; no shares issued or outstanding at December 31, 2021 and 2020	—	—
Common stock, par value \$0.0001; 1,600 shares authorized as of December 31, 2021 and 2020; 403 and 399 shares issued and outstanding as of December 31, 2021 and 2020, respectively	—	—
Additional paid-in capital	4,211	4,802
Accumulated other comprehensive (loss) income	(24)	3
Retained earnings (accumulated deficit)	9,958	(2,244)
Total stockholders' equity	14,145	2,561
Total liabilities and stockholders' equity	<u>\$ 24,669</u>	<u>\$ 7,337</u>

The accompanying notes are an integral part of these consolidated financial statements.

MODERNA, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In millions, except per share data)

	Years Ended December 31,		
	2021	2020	2019
Revenue:			
Product sales	\$ 17,675	\$ 200	\$ —
Grant revenue	735	529	12
Collaboration revenue	61	74	48
Total revenue	18,471	803	60
Operating expenses:			
Cost of sales	2,617	8	—
Research and development	1,991	1,370	496
Selling, general and administrative	567	188	110
Total operating expenses	5,175	1,566	606
Income (loss) from operations	13,296	(763)	(546)
Interest income	18	25	39
Other expense, net	(29)	(6)	(8)
Income (loss) before income taxes	13,285	(744)	(515)
Provision for (benefit from) income taxes	1,083	3	(1)
Net income (loss)	\$ 12,202	\$ (747)	\$ (514)
Earnings (loss) per share:			
Basic	\$ 30.31	\$ (1.96)	\$ (1.55)
Diluted	\$ 28.29	\$ (1.96)	\$ (1.55)
Weighted average common shares used in calculation of earnings (loss) per share:			
Basic	403	381	331
Diluted	431	381	331

The accompanying notes are an integral part of these consolidated financial statements.

MODERNA, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(In millions)

	Years Ended December 31,		
	2021	2020	2019
Net income (loss)	\$ 12,202	\$ (747)	\$ (514)
Other comprehensive (loss) income, net of tax			
Available-for-sales securities:			
Unrealized (losses) gains on available-for-sale debt securities	(42)	2	3
Less: net realized (gains) on available-for-sale securities reclassified to net income (loss)	(1)	(1)	—
Net (decrease) increase from available-for-sale debt securities	(43)	1	3
Cash flow hedges:			
Unrealized gains on derivative instruments	74	—	—
Less: net realized (gains) on derivative instruments reclassified to net income (loss)	(58)	—	—
Net increase from derivatives designated as hedging instruments	16	—	—
Total other comprehensive (loss) income	(27)	1	3
Comprehensive income (loss)	\$ 12,175	\$ (746)	\$ (511)

The accompanying notes are an integral part of these consolidated financial statements.

MODERNA, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(In millions)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	329	\$ —	\$ 2,538	\$ (1)	\$ (1,007)	\$ 1,530
Vesting of restricted common stock and restricted stock units	1	—	—	—	—	—
Exercise of options to purchase common stock	7	—	48	—	—	48
Purchase of common stock under employee stock purchase plan	—	—	3	—	—	3
Transition adjustment from adoption of ASC 606	—	—	—	—	28	28
Transition adjustment from adoption of ASC 842	—	—	—	—	(4)	(4)
Stock-based compensation	—	—	81	—	—	81
Other comprehensive income, net of tax	—	—	—	3	—	3
Net loss	—	—	—	—	(514)	(514)
Balance at December 31, 2019	<u>337</u>	<u>\$ —</u>	<u>\$ 2,670</u>	<u>\$ 2</u>	<u>\$ (1,497)</u>	<u>\$ 1,175</u>

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2019	337	\$ —	\$ 2,670	\$ 2	\$ (1,497)	\$ 1,175
Proceeds from public offering of common stock, net of issuance costs of \$2	48	—	1,853	—	—	1,853
Exercise of options to purchase common stock	14	—	179	—	—	179
Purchase of common stock under employee stock purchase plan	—	—	7	—	—	7
Stock-based compensation	—	—	93	—	—	93
Other comprehensive income, net of tax	—	—	—	1	—	1
Net loss	—	—	—	—	(747)	(747)
Balance at December 31, 2020	<u>399</u>	<u>\$ —</u>	<u>\$ 4,802</u>	<u>\$ 3</u>	<u>\$ (2,244)</u>	<u>\$ 2,561</u>

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Retained Earnings (Accumulated Deficit)	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2020	399	\$ —	\$ 4,802	\$ 3	\$ (2,244)	\$ 2,561
Exercise of options to purchase common stock	7	—	112	—	—	112
Purchase of common stock under employee stock purchase plan	—	—	12	—	—	12
Stock-based compensation	—	—	142	—	—	142
Other comprehensive loss, net of tax	—	—	—	(27)	—	(27)
Repurchase of common stock	(3)	—	(857)	—	—	(857)
Net income	—	—	—	—	12,202	12,202
Balance at December 31, 2021	403	\$ —	\$ 4,211	\$ (24)	\$ 9,958	\$ 14,145

The accompanying notes are an integral part of these consolidated financial statements.

MODERNA, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In millions)

	Years Ended December 31,		
	2021	2020	2019
Operating activities			
Net income (loss)	\$ 12,202	\$ (747)	\$ (514)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Stock-based compensation	142	93	81
Depreciation and amortization	232	31	31
Leased assets expensed	—	62	—
Amortization/accretion of investments	54	10	(4)
Deferred income taxes	(318)	—	—
Changes in assets and liabilities:			
Accounts receivable	(1,784)	(1,385)	7
Prepaid expenses and other assets	(489)	(241)	10
Inventory	(1,394)	(47)	—
Right-of-use assets, operating leases	(58)	(11)	(6)
Accounts payable	204	12	(24)
Accrued liabilities	989	388	(3)
Deferred revenue	2,824	3,842	(44)
Income taxes payable	876	—	—
Operating lease liabilities	17	12	13
Other liabilities	123	8	(6)
Net cash provided by (used in) operating activities	13,620	2,027	(459)
Investing activities			
Purchases of marketable securities	(12,652)	(2,956)	(1,145)
Proceeds from maturities of marketable securities	1,338	1,137	993
Proceeds from sales of marketable securities	3,105	215	169
Purchases of property and equipment	(284)	(68)	(32)
Investment in convertible notes	(30)	—	—
Net cash used in investing activities	(8,523)	(1,672)	(15)
Financing activities			
Proceeds from offerings of common stock, net of issuance costs	—	1,853	—
Proceeds from issuance of common stock through equity plans, net	124	186	51
Repurchase of common stock	(857)	—	—
Changes in financing lease liabilities	(140)	(6)	1
Net cash (used in) provided by financing activities	(873)	2,033	52
Net increase (decrease) in cash, cash equivalents and restricted cash	4,224	2,388	(422)
Cash, cash equivalents and restricted cash, beginning of year	2,636	248	670
Cash, cash equivalents and restricted cash, end of year	\$ 6,860	\$ 2,636	\$ 248
Supplemental cash flow information			
Cash paid for income taxes	\$ 480	\$ 1	\$ —
Cash paid for interest	\$ 14	\$ 9	\$ 6
Non-cash investing and financing activities			
Purchases of property and equipment included in accounts payable and accrued liabilities	\$ 111	\$ 18	\$ 5

The accompanying notes are an integral part of these consolidated financial statements.

MODERNA, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Description of Business

Moderna, Inc. (collectively, with its consolidated subsidiaries, any of Moderna, we, us, our or the Company) was incorporated in Delaware on July 22, 2016. We are the successor in interest to Moderna LLC, a limited liability company formed under the laws of the State of Delaware in 2013. Our principal executive office is located at 200 Technology Square, Cambridge, MA.

We are a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines to improve the lives of patients. mRNA medicines are designed to direct the body's cells to produce intracellular, membrane, or secreted proteins that have a therapeutic or preventive benefit with the potential to address a broad spectrum of diseases. Our platform builds on continuous advances in basic and applied mRNA science, delivery technology, and manufacturing, providing us the capability to pursue in parallel a robust pipeline of new development candidates. We are developing therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases, autoimmune diseases and cardiovascular diseases, independently and with our strategic collaborators.

On December 18, 2020, we received an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) for the emergency use of the Moderna COVID-19 Vaccine (also referred to as mRNA-1273 and marketed under the brand name Spikevax) in individuals 18 years of age or older. We have also received authorization for our COVID-19 vaccine from health agencies in more than 70 countries and from the World Health Organization (WHO). Additional authorizations are currently under review in other countries. In addition, we have received authorization for our COVID-19 vaccine for use in adolescents in the United Kingdom, European Union, Japan, Canada, Switzerland, Taiwan, Saudi Arabia, Australia, and the Philippines, and have pending applications for authorization to administer the vaccine to adolescents with regulatory agencies in the United States and other countries. In January 2022, we received full FDA approval for Spikevax to prevent COVID-19 in individuals 18 years of age and older in the United States. In February 2022, we received approval for the administration of Spikevax to children ages 6-11 in Australia and a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use for the administration of Spikevax in children ages 6-11 years.

2. Summary of Significant Accounting Policies

Basis of Presentation and Principles of Consolidation

Our consolidated financial statements are prepared in accordance with U.S. generally accepted accounting principles (GAAP). Any reference in these notes to applicable guidance is meant to refer to the authoritative accounting principles generally accepted in the United States as found in the Accounting Standard Codification (ASC) and Accounting Standards Updates (ASU) of the Financial Accounting Standards Board (FASB).

The consolidated financial statements include the Company and its subsidiaries. All intercompany transactions and balances have been eliminated in consolidation.

Use of Estimates

We have made estimates and judgments affecting the amounts reported in our consolidated financial statements and the accompanying notes. We base our estimates on historical experience and various relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting periods that are not readily apparent from other sources. Significant estimates relied upon in preparing these financial statements include, but are not limited to, revenue recognition, research and development expense, leases, fair value of financial instruments, derivative financial instruments, inventory, useful lives of property and equipment, stock-based compensation, income taxes, and our valuation allowance on our deferred tax assets. The actual results that we experience may differ materially from our estimates.

Segment Information

We have determined that our chief executive officer is the chief operating decision maker (CODM). The CODM reviews financial information presented on a consolidated basis. Resource allocation decisions are made by the CODM based on consolidated results. There are no segment managers who are held accountable by the CODM for operations, operating results, and planning for levels or components below the consolidated unit level. As such, we have concluded that we operate as one segment.

Revenue Recognition

On January 1, 2019, we adopted ASC 606 (*Revenue from Contracts with Customers*) using the modified retrospective transition method applied to those contracts which were not completed as of January 1, 2019. ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. To determine the appropriate amount of revenue to be recognized for arrangements that we determine are within the scope of ASC 606, we perform the following five steps (the five-step model): (i) identify the contract(s) with our customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when or as each performance obligation is satisfied.

Our revenue is primarily generated through product sales. We also generate grant revenue from government-sponsored and private organizations, and collaboration revenue through collaboration arrangements.

Product Sales

Product sales are associated with our COVID-19 vaccine supply agreements with the U.S. Government, other international governments, Gavi (on behalf of the COVAX Facility), and the African Union. These agreements generally do not include variable consideration, such as discounts, rebates or returns. Under these agreements, we are entitled to upfront deposits for our COVID-19 vaccine supply, initially recorded as deferred revenue. We recognize revenue from product sales, using the five-step model under ASC 606, based on the fixed price per dose according to the contracts when control of the product transfers to the customer and customer acceptance has occurred, unless such acceptance provisions are deemed perfunctory.

We pay distribution fees to certain customers in connection with the sales of our product. We record distribution fees paid to our customers as a reduction of revenue, unless the payment is for a distinct good or service from the customer and we can reasonably estimate the fair value of the goods or services received. If both conditions are met, we record the consideration paid to the customer as an operating expense. These costs are typically known at the time of sale, resulting in minimal adjustments subsequent to the period of sale. Such distribution fees were immaterial for the year ended December 31, 2021. We did not have any distribution fees for the years ended December 31, 2020 and 2019.

Grant Revenue

We have contracts with Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS); the U.S. government's Defense Advanced Research Projects Agency (DARPA); the Bill & Melinda Gates Foundation (Gates Foundation) and other government-sponsored and private organizations for research and development related activities that provide for payments for reimbursed costs, which may include overhead and general and administrative costs as well as a related profit margin. We recognize revenue from these contracts as we perform services under these arrangements when the funding is committed. Associated expenses are recognized when incurred as research and development expense. Revenues and related expenses are presented gross in the consolidated statements of operations as we have determined we are the primary obligor under the arrangements relative to the research and development services we perform as lead technical expert.

Collaboration Revenue

We have entered into several strategic collaborations and other similar arrangements with third parties for research and other licenses, development and commercialization of certain products and product candidates. Such arrangements provide for various types of payments to us, including upfront fees, funding of research and development services and preclinical and clinical material, technical, development, regulatory, and commercial milestone payments, licensing fees, option exercise fees, and royalty and earnout payments on product sales. Such payments are often not commensurate with the timing of revenue recognition and therefore result in deferral of revenue recognition. We recognize revenue based on the amount of the transaction price that is allocated to each respective performance obligation when or as the performance obligation is satisfied by transferring a promised good or service to the customer.

Cash and Cash Equivalents

We consider all highly liquid investments with an original maturity of 90 days or less from the date of purchase to be cash equivalents.

Restricted Cash

Restricted cash is composed of amounts held on deposit related to our lease arrangements. The funds are maintained in money market accounts and are recorded at fair value. We classify our restricted cash as either current or non-current based on the terms of the underlying lease arrangement.

Cash, Cash Equivalents and Restricted Cash shown in the Consolidated Statements of Cash Flows

The following table provides a reconciliation of cash, cash equivalents and restricted cash in the consolidated balance sheets that sum to the total of the same such amounts shown in the consolidated statements of cash flows (in millions):

	December 31,		
	2021	2020	2019
Cash and cash equivalents	\$ 6,848	\$ 2,624	\$ 236
Restricted cash ⁽¹⁾	—	1	1
Restricted cash, non-current	12	11	11
Total cash, cash equivalents and restricted cash shown in the consolidated statements of cash flows	<u>\$ 6,860</u>	<u>\$ 2,636</u>	<u>\$ 248</u>

⁽¹⁾ Included in prepaid expenses and other current assets in the consolidated balance sheets.

Investments

We invest our excess cash balances in marketable debt securities. We classify our investments in marketable debt securities as available-for-sale. We report available-for-sale investments at fair value at each balance sheet date, and include any unrealized holding gains and losses (the adjustment to fair value) in accumulated other comprehensive (loss) income, a component of stockholders' equity. Realized gains and losses are determined using the specific-identification method, and are included in other expense, net in our consolidated statements of operations. We classify our available-for-sale marketable securities as current or non-current based on each instrument's underlying effective maturity date and for which we have the intent and ability to hold the investment for a period of greater than 12 months. Marketable securities with maturities of less than 12 months are classified as current and are included in investments in the consolidated balance sheets. Marketable securities with maturities greater than 12 months for which we have the intent and ability to hold the investment for greater than 12 months are classified as non-current and are included in investments, non-current in the consolidated balance sheets.

We evaluate securities for impairment at the end of each reporting period. Impairment is evaluated considering numerous factors, and their relative significance varies depending on the situation. Factors considered include whether a decline in fair value below the amortized cost basis is due to credit-related factors or non-credit-related factors, the financial condition and near-term prospects of the issuer, and our intent and ability to hold the investment to allow for an anticipated recovery in fair value. A credit-related impairment is recognized as an allowance on the balance sheet with a corresponding adjustment to earnings. Any impairment that is not credit-related is recognized in other comprehensive (loss) income, net of applicable taxes.

Accounts Receivable and Allowance for Doubtful Accounts

We have accounts receivable amounts due from our product sales and related vaccine supply agreements and our grant agreements. We also have accounts receivable amounts due from strategic collaborators as a result of manufacturing and research and development services provided under collaboration arrangements, or milestones achieved, but not yet paid. Amounts payable to us are recorded as accounts receivable when our right to consideration is unconditional. To estimate the allowance for doubtful accounts, we make judgments about the creditworthiness of our customers based on ongoing credit evaluation and historical experience. There was no allowance for doubtful accounts at December 31, 2021 or 2020. There was no bad debt expense for the years ended December 31, 2021, 2020 or 2019.

Concentrations of Credit Risk

Financial instruments that subject us to significant concentrations of credit risk consist primarily of cash, cash equivalents, restricted cash, marketable securities, and accounts receivable. Our investment portfolio comprises money market funds and marketable debt securities, including U.S. Treasury securities, debt securities of U.S. government agencies and corporate entities and commercial paper. Our cash management and investment policy limits investment instruments to investment-grade securities with the objective to preserve capital and to maintain liquidity until the funds can be used in business operations. Bank accounts in the United States are insured by the Federal Deposit Insurance Corporation (FDIC) up to \$250,000. Our primary operating accounts significantly exceed the FDIC limits.

Significant Customers

Our accounts receivable are generally unsecured and are from customers in different countries. We generated revenue from product sales to the U.S. Government, other international governments, Gavi (on behalf of the COVAX Facility), the African Union, grants made by government-sponsored and private organizations, and to a lesser extent, strategic alliances in 2021 and 2020. Historically, we generated revenue primarily from strategic alliances.

A significant portion of our revenue to date has been generated from the following entities that accounted for more than 10% of total revenue and accounts receivable for the periods presented:

	Percentage of Revenue Years Ended December 31,			Percentage of Accounts Receivable December 31,	
	2021	2020	2019	2021	2020
European Commission	32 %	*	*	46 %	28 %
U.S. Government (excluding BARDA)	29 %	24 %	*	*	*
BARDA	*	65 %	13 %	16 %	22 %
Merck	*	*	61 %	*	*
Vertex	*	*	10 %	*	*
United Kingdom Government	*	*	*	*	11 %
South Korea Government	*	*	*	*	24 %

* - Represents an amount of less than 10%

Derivative Instruments and Hedging Activities

We record all derivatives on our consolidated balance sheets at fair value. The accounting for changes in the fair value of a derivative depends on whether the derivative has been designated and qualifies for hedge accounting. Derivatives designated and qualifying as a hedge of the exposure to variability in expected future cash flows, or other types of forecasted transactions, are considered cash flow hedges. Hedge accounting generally provides for the matching of the timing of gain or loss recognition on the hedging instrument with the recognition of the changes in the fair value of the hedged asset or liability that are attributable to the hedged risk in a fair value hedge or the earnings effect of the hedged forecasted transactions in a cash flow hedge.

The gains or losses resulting from changes in the fair value of cash flow hedges are initially recorded as a component of accumulated other comprehensive (loss) income (AOCI) in stockholders' equity and subsequently reclassified to product sales in the period during which the hedged transaction affects earnings. In the event the underlying forecasted transaction does not occur, or it becomes probable that it will not occur, within the defined hedge period, we reclassify the gains or losses on the related cash flow hedge from AOCI to other expense, net, in our consolidated statements of operations. We may enter into derivative contracts that are intended to economically hedge certain risk, even though hedge accounting does not apply or we elect not to apply hedge accounting. Gains or losses associated with foreign currency derivatives that are not designated as hedging instruments for accounting purposes are recorded within other expense, net, in our consolidated statements of operations.

Fair Value Measurements

Fair value is defined as the price that would be received from selling an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. When determining the fair value measurements for assets and liabilities, which are required to be recorded at fair value, we consider the principal or most advantageous market in which we would transact and the market-based risk measurements or assumptions that market participants would use in pricing the asset or liability, such as risks inherent in valuation techniques, transfer restrictions and credit risk. ASC 820 (*Fair Value Measurement*) establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and our assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from our independent sources. Unobservable inputs are inputs that reflect our assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances. The following fair value hierarchy is used to classify assets and liabilities based on the observable inputs and unobservable inputs used to value the assets and liabilities:

- Level 1: Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities;

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- Level 2: Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liability; or
- Level 3: Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Our cash equivalents and marketable securities are reported at fair value determined using Level 1 and Level 2 inputs (Note 6). The fair value of our foreign currency forward contracts is calculated using Level 2 inputs, which include currency spot rates, forward rates, interest rate curve and credit or non-performance risk (Note 7). We do not have any non-financial assets or liabilities that should be recognized or disclosed at fair value on a recurring basis at December 31, 2021, 2020, and 2019.

We maintained letters of credit of \$12 million as of December 31, 2021 and 2020, related to our lease arrangements, which are secured by money market accounts in accordance with certain of our lease agreements. The amounts are recorded at fair value using Level 1 inputs and included as restricted cash in our consolidated balance sheets.

Inventory

Inventory is recorded at the lower of cost or net realizable value, with cost determined using first-in, first-out and average cost methods for different components of inventory. We periodically review the composition of inventory in order to identify excess, obsolete, slow-moving or otherwise unsaleable items. If unsaleable items are observed and there are no alternate uses for the inventory, we will record a write-down to net realizable value in the period that the decline in value is first recognized through a charge to cost of sales. The determination of whether inventory costs will be realizable requires estimates by management. If actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required. The determination of net realizable value requires judgment including consideration of many factors, such as estimates of future product demand, product net selling prices, current and future market conditions and potential product obsolescence, among others.

Prior to an initial regulatory approval for our investigational medicines, we expense costs relating to raw materials and production of inventory as research and development expense in our consolidated statements of operations, in the period incurred. Upon the authorization of distribution and use of our COVID-19 vaccine under an EUA in December 2020, we began to capitalize inventory costs associated with our COVID-19 vaccine, as it was determined that inventory costs incurred subsequent to the EUA had a probable future economic benefit.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation. Depreciation is calculated using the straight-line method over the estimated useful lives of the assets. The estimated useful lives of property and equipment are described below:

	Estimated Useful Life
Laboratory equipment	5 years
Leasehold improvements	Lesser of estimated useful life of improvement or remaining life of related lease
Computer equipment and software	3 years
Internally developed software	3 years
Furniture, fixtures and other	5 years
Right of use asset, financing	Lease term

Construction in progress includes direct costs related to the construction of various property and equipment, including leasehold improvements, and is stated at original cost. Construction in progress includes costs incurred under construction contracts including project management services, engineering services, design services and development, construction services and other construction-related fees and services. Such costs are not depreciated until the asset is completed and placed into service. Once the asset is placed into service, these capitalized costs will be allocated to certain property and equipment categories and will be depreciated over the estimated useful life of the underlying assets.

Expenditures for maintenance and repairs are charged to expense as incurred. Upon retirement or sale, the cost of the assets disposed of, and the related accumulated depreciation, are removed from the accounts, and any resulting gain or loss is recorded to other expense, net in our consolidated statements of operations.

Impairment of Long-Lived Assets

We evaluate our long-lived assets, which consist of property and equipment, to determine if facts and circumstances indicate that the carrying amount of assets may not be recoverable. If such facts and circumstances exist, we assess the recoverability of the long-lived assets by comparing the projected future undiscounted net cash flows associated with the related asset or group of assets over their remaining lives against their respective carrying amounts. If such review indicates that such cash flows are not expected to be sufficient to recover the recorded value of the assets, the assets are written down to their estimated fair values based on the expected discounted future cash flows attributable to the assets or based on appraisals. Impairment expenses for the years ended December 31, 2021, 2020 and 2019 were immaterial.

Leases

Leases are classified at their commencement date, which is defined as the date on which the lessor makes the underlying asset available for use by the lessee, as either operating or finance leases based on the economic substance of the agreement. We recognize lease right-of-use assets and related liabilities in our consolidated balance sheets for both operating and finance leases. Lease liabilities are measured at the lease commencement date as the present value of the future lease payments using the interest rate implicit in the lease. If the rate implicit is not readily determinable, we will utilize our incremental borrowing rate as of the lease commencement date. Lease right-of-use assets are measured as the lease liability plus initial direct costs and prepaid lease payments less lease incentives. The lease term is the non-cancelable period of the lease and includes options to extend or terminate the lease when it is reasonably certain that an option will be exercised.

We recognize operating lease cost in operating expenses in our consolidated statements of operations, inclusive of rent escalation provisions and rent holidays, on a straight-line basis over the respective lease term. For our finance leases, we recognize depreciation expense associated with the leased asset acquired and recognize interest expense related to the portion of the financing in our consolidated statements of operations.

We do not separate non-lease components from lease components for all classes of underlying assets. We do not recognize right-of-use assets and lease liabilities for leases with a lease term of 12 months or less. Instead, these lease payments are recognized in profit or loss on a straight-line basis over the lease term.

Cost of Sales

Cost of sales includes cost of raw materials, production, transportation, freight and indirect overhead costs associated with our product sales during the period and third-party royalties on net sales of our product. Cost of sales also includes adjustments for excess and obsolete inventory to the extent management determines that the cost cannot be recovered based on estimates about future demand.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, contract services, and other outside costs. The value of goods and services received from contract research organizations and contract manufacturing organizations in the reporting period are estimated based on the level of services performed, and progress in the period in cases when we have not received an invoice from the supplier.

Equipment or facilities that are acquired or constructed for research and development activities and that have alternative future uses, in research and development projects or otherwise, should be capitalized and depreciated as tangible assets. However, the costs of equipment or facilities that are acquired or constructed and intangibles that are purchased from others for a particular research and development project and that have no alternative future uses and therefore no separate economic values are considered research and development costs and are expensed when incurred.

Stock-Based Compensation

We issue stock-based awards to employees and non-employees, generally in the form of stock options, restricted stock units (RSUs), and performance stock units (PSUs). We account for our stock-based compensation awards in accordance with ASC 718 (*Compensation—Stock Compensation*). Most of our stock-based awards have been made to employees. We measure compensation cost for equity awards at their grant-date fair value and recognize compensation expense over the requisite service period, which is generally the vesting period, on a straight-line basis. The grant date fair value of stock options is estimated using the Black-Scholes option pricing model, which requires management to make assumptions with respect to the fair value of our common stock on the grant date, including the expected term of the award, the expected volatility of our stock, calculated based on a period of time generally commensurate with the expected term of the award, risk-free interest rates and expected dividend yields of our stock. The grant date fair value of RSUs is estimated based on the fair value of our underlying common stock. For performance-based stock awards, we recognize stock-based compensation expense over the requisite service period using the accelerated attribution method when achievement is probable. We classify stock-based compensation expense in our consolidated statements of operations in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified. We made an accounting policy election to recognize forfeitures of stock-based awards as they occur.

Income Taxes

We account for income taxes based on an asset and liability approach. We recognize deferred tax assets and liabilities for the expected future tax consequences of temporary differences between the financial reporting and tax bases of assets and liabilities. These differences are measured using the enacted statutory tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided when the expected realization of deferred tax assets does not meet a "more likely than not" criterion. We make estimates and judgments about our future taxable income that are based on assumptions that are consistent with our plans and estimates. Should the actual amounts differ from our estimates, the amount of our valuation allowance could be materially impacted. Changes in these estimates may result in significant increases or decreases to our tax provision in a period in which such estimates are changed, which in turn would affect net income or loss. We recognize tax benefits from uncertain tax positions if we believe the position is more likely than not to be sustained on examination by the taxing authorities based on the technical merits of the position. We make adjustments to these tax reserves when facts and circumstances change, such as the closing of a tax audit or the refinement of an estimate. The provision for income taxes includes the effects of any reserves for uncertain tax positions, as well as the related net interest and penalties.

Earnings (Loss) per Share

We calculate diluted net earnings (loss) per share attributable to common stockholders by dividing net earnings (loss) by the weighted average number of common shares outstanding after giving consideration to the dilutive effect of restricted common stock and stock options that are outstanding during the period. For periods in which we have generated a net loss, the basic and diluted net loss per share attributable to common stockholders are the same, as the inclusion of the potentially dilutive securities would be anti-dilutive.

Comprehensive Income (Loss)

Comprehensive income (loss) includes net income (loss) and other comprehensive income (loss) for the period. Other comprehensive income (loss) consists of unrealized gains and losses on our investments and derivatives designated as hedging instruments. Total comprehensive income (loss) for all periods presented has been disclosed in the consolidated statements of comprehensive income (loss).

The components of accumulated other comprehensive (loss) income for the years ended December 31, 2021 and 2020 were as follows (in millions):

	Unrealized Gain (Loss) on Available-for-Sale Debt Securities	Net Unrealized Gains on Derivatives Designated As Hedging Instruments	Total
Accumulated other comprehensive income, balance at December 31, 2019	\$ 2	\$ —	\$ 2
Other comprehensive income	1	—	1
Accumulated other comprehensive income, balance at December 31, 2020	3	—	3
Other comprehensive loss	(43)	16	(27)
Accumulated other comprehensive loss, balance at December 31, 2021	\$ (40)	\$ 16	\$ (24)

Recently Issued Accounting Standards Not Yet Adopted

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies and adopted by us as of the specified effective date. Unless otherwise discussed, we believe that the impact of recently issued standards that are not yet effective will not have a material impact on our consolidated financial statements and disclosures.

3. Product Sales

Product sales are primarily associated with our COVID-19 vaccine supply agreements with the U.S. Government, other international governments, Gavi (on behalf of the COVAX Facility), and the African Union.

Product sales by customer geographic location was as follows (in millions):

	Year Ended December 31,	
	2021	2020
United States	\$ 5,393	\$ 194
Europe	6,834	—
Rest of world ⁽¹⁾	5,448	6
Total	\$ 17,675	\$ 200

⁽¹⁾ Includes product sales recognized under the agreement with Gavi as Gavi facilitates a fair allocation and distribution of our COVID-19 vaccine around the world.

There were no product sales in 2019. As of December 31, 2021 and 2020, our COVID-19 vaccine was our only commercial product authorized for use.

As of December 31, 2021 and 2020, we had deferred revenue of \$6.7 billion and \$3.8 billion, respectively, related to customer deposits. We expect \$6.2 billion of our deferred revenue related to customer deposits as of December 31, 2021 to be realized in less than one year. Timing of product manufacturing, delivery and receipt of marketing approval will determine the period in which revenue is recognized.

4. Grant Revenue

In September 2020, we entered into an agreement with the DARPA for an award of up to \$56 million to fund development of a mobile manufacturing prototype leveraging our existing manufacturing technology that is capable of rapidly producing vaccines and therapeutics. As of December 31, 2021, the committed funding, net of revenue earned was \$2 million. An additional \$42 million of funding will be available if DARPA exercises additional contract options.

In April 2020, we entered into an agreement with BARDA for an award of up to \$483 million to accelerate development of mRNA-1273, our vaccine candidate against COVID-19. In July 2020, we amended our agreement with BARDA to provide for an additional commitment of up to \$472 million to support late-stage clinical development of mRNA-1273, including the execution of a 30,000 participant Phase 3 study in the U.S. We further amended the agreement in March 2021 to provide for an additional commitment of \$63 million to further support late-stage clinical development, including Phase 2/3 mRNA-1273 pediatric studies. In April 2021, we entered into a further amendment to the BARDA agreement, increasing the amount of potential reimbursements by \$236 million in connection with costs associated with the Phase 3 clinical trials for mRNA-1273 and pharmacovigilance efforts. In June 2021, the agreement with BARDA was further amended to award additional funding of \$144 million to support pediatric clinical trials for mRNA-1273. The maximum award from BARDA, inclusive of the 2020 and 2021 amendments, was \$1.4 billion. Under the terms of the agreement, BARDA will fund the advancement of mRNA-1273 to FDA licensure. All contract options have been exercised. As of December 31, 2021, the remaining available funding, net of revenue earned was \$189 million.

In September 2016, we received from BARDA an award of up to \$126 million, subsequently adjusted to \$117 million in 2021, to help fund our Zika vaccine program. Three of the four contract options have been exercised. As of December 31, 2021, the remaining available funding, net of revenue earned was \$48 million, with an additional \$8 million available if the final contract option is exercised.

In January 2016, we entered a global health project framework agreement with the Gates Foundation to advance mRNA-based development projects for various infectious diseases, including human immunodeficiency virus (HIV). As of December 31, 2021, the

available funding, net of revenue earned was \$7 million, with up to an additional \$80 million available if additional follow-on projects are approved.

The following table summarizes grant revenue for the periods presented (in millions):

	Years Ended		
	2021	2020	2019
BARDA	\$ 713	\$ 522	\$ 8
Other grant revenue	22	7	4
Total grant revenue	\$ 735	\$ 529	\$ 12

5. Collaboration Agreements

AstraZeneca – Strategic Alliances in Cardiovascular and Oncology

2013 Option Agreement and Services and Collaboration Agreement, amended and restated in 2018

In March 2013, we entered into an Option Agreement, the AZ Option Agreement, and a related Services and Collaboration Agreement (2013 AZ Agreements), the AZ Services Agreement, with AstraZeneca, which were amended and restated in June 2018 (2018 A&R Agreements). Under the 2018 A&R Agreements, we granted AstraZeneca certain exclusive rights and licenses, and options to obtain exclusive rights to develop and commercialize potential therapeutic mRNA medicines directed at certain targets for the treatment of cardiovascular and cardiometabolic diseases and cancer, and agreed to provide related services to AstraZeneca. The activities to be performed by the parties under the 2018 A&R Agreements are limited to defined biological targets in the cardiovascular and cardiometabolic fields and one defined target in the cancer field.

As of the effective date of the 2013 AZ Agreements, AstraZeneca made upfront cash payments to us totaling \$240 million in exchange for the acquired options and our performance of certain research-related services, each as described above. Under the 2018 A&R Agreements, we are entitled to receive, on a product-by-product basis, payments for achievement of certain development, regulatory and commercial milestones, as well as earn-out payments on worldwide net sales of products ranging from a high-single digit percentage to 12%, subject to certain reductions, with an aggregate minimum floor.

In 2016, AstraZeneca exercised a product option under the 2013 AZ Agreements to obtain exclusive rights to develop and commercialize with respect to AstraZeneca's VEGF-A product (AZD8601). It is currently being developed in a Phase 2 clinical trial.

2016 Strategic Alliance with AstraZeneca – IL-12

In January 2016, we entered into a Strategic Drug Development Collaboration and License Agreement (2016 AZ Agreement) with AstraZeneca to discover, develop and commercialize potential mRNA medicines for the treatment of a range of cancers. Under the terms of the 2016 AZ Agreement, we and AstraZeneca have agreed to work together on an immuno-oncology program focused on the intratumoral delivery of a potential mRNA medicine to make the IL-12 protein. During a limited period of time, each party had an opportunity to propose additional discovery programs to be conducted under the 2016 AZ Agreement. We are responsible for conducting and funding all discovery and preclinical development activities under the 2016 AZ Agreement in accordance with an agreed upon discovery program plan for the IL-12 program and any other discovery program the parties agree to conduct under the 2016 AZ Agreement.

Merck – Strategic Alliances in Infectious Diseases and Cancer Vaccines

2016 Cancer Vaccine Strategic Alliance-Personalized mRNA Cancer Vaccines

In June 2016, we entered into a personalized mRNA cancer vaccines (PCV) Collaboration and License Agreement with Merck (PCV Agreement), to develop and commercialize PCVs for individual patients using our mRNA vaccine and formulation technology. Under the strategic alliance, we identify genetic mutations present in a particular patient's tumor cells, synthesize mRNA for these mutations, encapsulate the mRNA in one of our proprietary LNPs and administer to each patient a unique mRNA cancer vaccine designed to specifically activate the patient's immune system against her or his own cancer cells.

Pursuant to the PCV Agreement, we are responsible for designing and researching PCVs, providing manufacturing capacity and manufacturing PCVs, and conducting Phase 1 and Phase 2 clinical trials for PCVs, alone and in combination with KEYTRUDA (pembrolizumab), Merck's anti-PD-1 therapy, all in accordance with an agreed upon development plan and budget and under the

oversight of a committee comprised of equal representatives of each party. The parties have entered into a clinical quality agreement with respect to Moderna's manufacture and supply activities. We received an upfront payment of \$200 million from Merck.

2018 Expansion of the Cancer Vaccine Strategic Alliance-Shared Neoepitope Cancer Vaccines

In April 2018, we and Merck agreed to expand our cancer vaccine strategic alliance to include the development and commercialization of our KRAS vaccine development candidate, mRNA-5671 or V941, and potentially other shared neoantigen mRNA cancer vaccines (SAVs). We preclinically developed mRNA-5671 prior to its inclusion in the cancer vaccine strategic alliance and it is comprised of a novel mRNA construct designed by us and encapsulated in one of our proprietary LNPs. The PCV Agreement was amended and restated to include the new SAV strategic alliance (PCV/SAV Agreement).

We have granted Merck certain licenses and we and Merck have agreed to certain exclusivity obligations with respect to SAVs and particular SAV programs, which obligations are subject to termination or expiration upon certain triggering events. Under the PCV/SAV Agreement, Merck will be responsible for conducting Phase 1 and Phase 2 clinical trials for mRNA-5671 and for all costs associated with such activities, in accordance with a jointly agreed development plan and budget, and we will be responsible for manufacturing and supplying all mRNA-5671 required to conduct such trials and for all costs and expenses associated with such manufacture and supply. Under the PCV/SAV Agreement, our budgeted commitment for PCV increased to \$243 million. Until the expiration of a defined period of time following the completion of Phase 1 and Phase 2 clinical trials for mRNA-5671 under the PCV/SAV Agreement and our delivery of an associated data package to Merck, Merck has the right to elect to participate in future development and commercialization of mRNA-5671 by making a participation payment to us. In connection with the amendment of the PCV Agreement to include the development and commercialization of mRNA-5671 and potentially other SAVs, Merck made a contemporaneous equity investment in our Series H redeemable convertible preferred stock, resulting in gross proceeds of \$125 million, of which \$13 million was determined to be a premium and recorded to deferred revenue. In December 2021, Merck elected to terminate the Merck participation election with respect to the joint SAV program.

Vertex – Strategic Alliance in Cystic Fibrosis

2016 Strategic Alliance in Cystic Fibrosis

In July 2016, we entered into a Strategic Collaboration and License Agreement (Vertex Agreement), with Vertex Pharmaceuticals Incorporated, and Vertex Pharmaceuticals (Europe) Limited, together, Vertex. The Vertex Agreement, which was amended in July 2019 (2019 Vertex Amendment), is aimed at the discovery and development of potential mRNA medicines for the treatment of cystic fibrosis (CF) by enabling cells in the lungs of people with CF to produce functional cystic fibrosis transmembrane conductance regulator (CFTR) proteins. Pursuant to the Vertex Agreement, we lead discovery efforts during an initial research period that currently extends until August 2022, leveraging our Platform technology and mRNA delivery expertise along with Vertex's scientific experience in CF biology and the functional understanding of CFTR. Vertex is responsible for conducting development and commercialization activities for candidates and products that arise from the strategic alliance, including the costs associated with such activities. Subject to customary "back-up" supply rights granted to Vertex, we exclusively manufacture (or have manufactured) mRNA for preclinical, clinical and commercialization purposes.

2020 Strategic Alliance in Cystic Fibrosis

In September 2020, we entered into a new Strategic Collaboration and License Agreement with Vertex (Vertex 2020 Agreement). The Vertex 2020 Agreement is aimed at the discovery and development of potential medicines to treat CF by delivering gene-editing therapies to lung cells to facilitate production of functional CFTR proteins. The three-year research period of the Vertex 2020 Agreement will initially focus on the identification and optimization of novel LNPs and mRNAs that can deliver gene-editing therapies to cells in the lungs. Following the initial three-year period, Vertex is responsible for conducting development and commercialization activities for candidates and products that arise from the strategic alliance, including the costs associated with such activities. Vertex is also obligated to pay us for research services in connection with our performance of certain activities in accordance with a jointly agreed research plan. Subject to customary "back-up" supply rights granted to Vertex, under the agreement, we are the exclusive manufacturer of related mRNA and LNPs for preclinical, clinical, and commercialization purposes.

The following table summarizes our total consolidated net revenue from our strategic collaborators for the periods presented (in millions):

Collaboration Revenue by Strategic Collaborator:	Years Ended December 31,		
	2021	2020	2019
AstraZeneca	\$ 7	\$ 33	\$ 5
Merck	23	26	37
Vertex	26	15	6
Other	5	—	—
Total collaboration revenue	<u>\$ 61</u>	<u>\$ 74</u>	<u>\$ 48</u>

The following table presents changes in the balances of our receivables and contract liabilities related to our strategic collaboration agreements during the year ended December 31, 2021 (in millions):

	December 31, 2020	Additions	Deductions	December 31, 2021
Contract Assets:				
Accounts receivable	\$ 6	\$ 26	\$ (23)	\$ 9
Contract Liabilities:				
Deferred revenue	\$ 240	\$ 27	\$ (63)	\$ 204

As of December 31, 2021, the aggregated amount of the transaction price allocated to performance obligations under our collaboration agreements that are unsatisfied or partially unsatisfied was \$286 million.

In addition to the collaborative arrangements mentioned above, we have other collaborative and licensing arrangements that we do not consider to be individually significant to our business at this time. Pursuant to these agreements, we may be required to make upfront payments and payments upon achievement of various development, regulatory and commercial milestones, which in the aggregate could be significant. Future milestone payments, if any, will be reflected in our consolidated financial statements when the corresponding events become probable. In addition, we may be required to pay significant royalties on future sales if products related to these arrangements are commercialized.

6. Financial Instruments and Fair Value Measurements

Cash and Cash Equivalents and Investments

The following tables summarize our cash and available-for-sale securities by significant investment category at December 31, 2021 and 2020 (in millions):

December 31, 2021							
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Current Marketable Securities	Non- Current Marketable Securities
Cash and cash equivalents	\$ 6,848	\$ —	\$ —	\$ 6,848	\$ 6,848	\$ —	\$ —
Available-for-sale:							
Certificates of deposit	80	—	—	80	—	80	—
U.S. treasury bills	479	—	—	479	—	479	—
U.S. treasury notes	6,595	—	(31)	6,564	—	1,984	4,580
Corporate debt securities	3,508	—	(20)	3,488	—	1,323	2,165
Government debt securities	112	—	(1)	111	—	13	98
Total	<u>\$ 17,622</u>	<u>\$ —</u>	<u>\$ (52)</u>	<u>\$ 17,570</u>	<u>\$ 6,848</u>	<u>\$ 3,879</u>	<u>\$ 6,843</u>
December 31, 2020							
	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value	Cash and Cash Equivalents	Current Marketable Securities	Non- Current Marketable Securities
Cash and cash equivalents	\$ 2,624	\$ —	\$ —	\$ 2,624	\$ 2,624	\$ —	\$ —
Available-for-sale:							
Certificates of deposit	239	—	—	239	—	215	24
U.S. treasury bills	492	—	—	492	—	492	—
U.S. treasury notes	87	—	—	87	—	38	49
Corporate debt securities	1,788	4	—	1,792	—	1,239	553
Government debt securities	13	—	—	13	—	—	13
Total	<u>\$ 5,243</u>	<u>\$ 4</u>	<u>\$ —</u>	<u>\$ 5,247</u>	<u>\$ 2,624</u>	<u>\$ 1,984</u>	<u>\$ 639</u>

The amortized cost and estimated fair value of marketable securities, by contractual maturity at December 31, 2021 and 2020 were as follows (in millions):

	December 31, 2021	
	Amortized Cost	Estimated Fair Value
Due in one year or less	\$ 3,882	\$ 3,879
Due after one year through five years	6,892	6,843
Total	\$ 10,774	\$ 10,722

	December 31, 2020	
	Amortized Cost	Estimated Fair Value
Due in one year or less	\$ 1,981	\$ 1,984
Due after one year through five years	638	639
Total	\$ 2,619	\$ 2,623

In accordance with our investment policy, we place investments in investment grade securities with high credit quality issuers, and generally limit the amount of credit exposure to any one issuer. We evaluate securities for impairment at the end of each reporting period. We did not record any impairment charges related to our available-for-sale securities during the years ended December 31, 2021, 2020, and 2019. We did not recognize any credit-related allowance to available-for-sale securities as of the years ended December 31, 2021 and 2020.

The following table summarizes the amount of gross unrealized losses and the estimated fair value for our available-for-sale securities in an unrealized loss position by length of time the securities have been in an unrealized loss position at December 31, 2021 (in millions):

	Less than 12 Months		12 Months or More		Total	
	Gross Unrealized Losses	Estimated Fair Value	Gross Unrealized Losses	Estimated Fair Value	Gross Unrealized Losses	Estimated Fair Value
As of December 31, 2021:						
U.S. treasury bills	\$ —	\$ 329	\$ —	\$ —	\$ —	\$ 329
U.S. treasury notes	(31)	6,332	—	—	(31)	6,332
Corporate debt securities	(20)	2,573	—	1	(20)	2,574
Government debt securities	(1)	112	—	—	(1)	112
Total	\$ (52)	\$ 9,346	\$ —	\$ 1	\$ (52)	\$ 9,347

As of December 31, 2020, we did not have material gross unrealized losses. We neither intend to sell these investments nor conclude that we are more-likely-than-not that we will have to sell them before recovery of their carrying values. We also believe that we will be able to collect both principal and interest amounts due to us at maturity.

Assets and Liabilities Measured at Fair Value on a Recurring Basis

The following tables summarize our financial assets measured at fair value on a recurring basis as of December 31, 2021 and 2020 (in millions):

	Fair value at December 31, 2021	Fair Value Measurement Using	
		Level 1	Level 2
Assets:			
Money market funds	\$ 2,329	\$ 2,329	\$ —
Certificates of deposit	80	—	80
U.S. treasury bills	479	—	479
U.S. treasury notes	6,564	—	6,564
Corporate debt securities	3,488	—	3,488
Government debt securities	111	—	111
Derivative instruments (Note 7)	21	—	21
Total	<u>\$ 13,072</u>	<u>\$ 2,329</u>	<u>\$ 10,743</u>
Liabilities:			
Derivative instruments (Note 7)	<u>\$ 7</u>	<u>\$ —</u>	<u>\$ 7</u>

	Fair value at December 31, 2020	Fair Value Measurement Using	
		Level 1	Level 2
Assets:			
Money market funds	\$ 660	\$ 660	\$ —
Certificates of deposit	239	—	239
U.S. treasury bills	492	—	492
U.S. treasury notes	87	—	87
Corporate debt securities	1,792	—	1,792
Government debt securities	13	—	13
Total	<u>\$ 3,283</u>	<u>\$ 660</u>	<u>\$ 2,623</u>

During the years ended December 31, 2021 and 2020, we did not have non-financial assets or liabilities measured at fair value on a recurring basis.

7. Derivative Financial Instruments

We transact business in various foreign currencies and have international sales and expenses denominated in foreign currencies. Therefore, we are exposed to certain risks arising from both our business operations and economic conditions. Our risk management strategy includes the use of derivative financial instruments to hedge foreign currency exchange rate fluctuations on monetary assets or liabilities denominated in foreign currencies. We do not enter into derivative financial contracts for speculative or trading purposes. We do not believe that we are exposed to more than a nominal amount of credit risk in our foreign currency hedges, as counterparties are large, global and well-capitalized financial institutions. We classify cash flows from our derivative transactions as cash flows from operating activities in our consolidated statements of cash flows.

Cash Flow Hedges

We mitigate the foreign exchange risk arising from the fluctuations in foreign currency denominated product sales in Euro through a foreign currency cash flow hedging program, using forward contracts and foreign currency options that do not exceed 15 months in duration. We hedge these cash flow exposures to reduce the risk that our earnings and cash flows will be adversely affected by changes in exchange rates. To receive hedge accounting treatment, all hedging relationships are formally documented at the inception of the hedge, and the hedges must be highly effective in offsetting changes to future cash flows on hedged transactions. The derivative assets or liabilities associated with our hedging activities are recorded at fair value in other current assets or other current liabilities, respectively, in our consolidated balance sheets. The gains or losses resulting from changes in the fair value of these hedges are initially recorded as a component of AOCI in stockholders' equity and subsequently reclassified to product sales in the period during which the hedged transaction affects earnings. In the event the underlying forecasted transaction does not occur, or it becomes

probable that it will not occur, within the defined hedge period, we reclassify the gains or losses on the related cash flow hedge from AOCI to other expense, net, in our consolidated statements of operations. We evaluate hedge effectiveness at the inception of the hedge prospectively, and on an on-going basis both retrospectively and prospectively. If we do not elect hedge accounting, or the contract does not qualify for hedge accounting treatment, the changes in fair value from period to period are recorded as a component of other expense, net, in our consolidated statements of operations. As of December 31, 2021, we had net deferred gains of \$21 million on our foreign currency forward contracts included in AOCI that are expected to be recognized into product sales within the next 12 months.

Balance Sheet Hedges

We enter into foreign currency forward contracts to hedge fluctuations associated with foreign currency denominated monetary assets and liabilities, primarily accounts receivable, accounts payable, and lease liabilities in Euro and Swiss Franc, that are not designated for hedge accounting treatment. Therefore, these forward contracts are accounted for as derivatives whereby the fair value of the contracts are reported as other current assets or other current liabilities on our consolidated balance sheets, and gains and losses resulting from changes in the fair value are recorded as a component of other expense, net, in our consolidated statements of operations. The gains and losses on these foreign currency forward contracts generally offset the gains and losses in the underlying foreign currency denominated assets and liabilities, which are also recorded to other expense, net, in our consolidated statements of operations.

Total gross notional amount and fair value for foreign currency derivatives were as follows (in millions):

		December 31, 2021	
		Notional Amount	Fair Value
		Asset ⁽¹⁾	Liability ⁽²⁾
Derivatives designated as cash flow hedging instruments:			
Foreign currency forward contracts	\$ 565	\$ 20	\$ —
Derivatives not designated as hedging instruments:			
Foreign currency forward contracts	1,370	1	7
Total derivatives	\$ 1,935	\$ 21	\$ 7
December 31, 2020			
		Asset ⁽¹⁾	Liability ⁽²⁾
Derivatives not designated as hedging instruments			
Foreign currency forward contracts	\$ 368	\$ —	\$ —
Total	\$ 368	\$ —	\$ —

⁽¹⁾ As presented in the consolidated balance sheet within prepaid expenses and other current assets.

⁽²⁾ As presented in the consolidated balance sheets within other current liabilities.

Gains on our foreign currency derivatives, net of tax, recognized in our consolidated statements of comprehensive income (loss) for the year ended December 31, 2021 was as follows (in millions):

	Year Ended December 31, 2021
Derivatives in cash flow hedging relationships:	
Foreign currency forward contracts	\$ 74

The effect of derivative instruments in our consolidated statements of operations for the year ended December 31, 2021 was as follows (in millions):

	Statement of Operations Classification	Year Ended December 31, 2021
Derivatives in cash flow hedging relationships:		
Foreign currency forward contracts		
Net gains reclassified from AOCI into income	Product sales	\$ 58
Derivatives not designated as hedging instruments:		
Foreign currency forward contracts		
Net realized and unrealized (losses)	Other expense, net	\$ (8)

There were immaterial hedging gains and losses for the year ended December 31, 2020 and no hedging gains or losses for the year ended December 31, 2019.

8. Inventory

Inventory as of December 31, 2021 and 2020 consisted of the following (in millions):

	December 31, 2021	December 31, 2020
Raw materials	\$ 870	\$ 37
Work in progress	338	9
Finished goods	233	1
Total inventory	<u>\$ 1,441</u>	<u>\$ 47</u>

9. Property and Equipment

Property and equipment, net as of December 31, 2021 and 2020 consisted of the following (in millions):

	December 31,	
	2021	2020
Laboratory equipment	\$ 175	\$ 121
Leasehold improvements	313	180
Furniture, fixtures and other	11	5
Computer equipment and software	16	13
Internally developed software	9	7
Right-of-use asset, financing	857	56
Construction in progress	212	35
	<u>1,593</u>	<u>417</u>
Less: Accumulated depreciation	<u>(352)</u>	<u>(120)</u>
Property and equipment, net	<u>\$ 1,241</u>	<u>\$ 297</u>

Depreciation and amortization expense for the years ended December 31, 2021, 2020, and 2019 was \$232 million, \$31 million, and \$31 million, respectively.

10. Other Balance Sheet Components

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets, as of December 31, 2021 and 2020 consisted of the following (in millions):

	December 31,	
	2021	2020
Down payments to manufacturing vendors	\$ 405	\$ 217
Other prepaid expenses	126	7
Value added tax receivable	70	7
Derivative assets	21	—
Tenant improvement allowance receivable	51	10
Other current assets	55	11
Prepaid expenses and other current assets	<u>\$ 728</u>	<u>\$ 252</u>

Accrued Liabilities

Accrued liabilities, as of December 31, 2021 and 2020 consisted of the following (in millions):

	December 31,	
	2021	2020
Clinical trials	\$ 283	\$ 98
Raw materials	260	78
Royalties	241	—
Development operations	137	29
Manufacturing	227	53
Other external goods and services	79	92
Compensation-related	126	95
Other	119	25
Accrued liabilities	<u>\$ 1,472</u>	<u>\$ 470</u>

Other Current Liabilities

Other current liabilities, as of December 31, 2021 and 2020 consisted of the following (in millions):

	December 31,	
	2021	2020
Lease liabilities - financing (Note 11)	\$ 165	\$ 24
Lease liabilities - operating (Note 11)	46	6
Other	14	4
Other current liabilities	<u>\$ 225</u>	<u>\$ 34</u>

Deferred Revenue

The following table summarizes the activities in deferred revenue during the year ended December 31, 2021 (in millions):

	December 31, 2020	Additions	Deductions	December 31, 2021
Product sales	\$ 3,799	\$ 11,657	\$ (8,798)	\$ 6,658
Grant revenue	5	12	(11)	6
Collaboration revenue	240	27	(63)	204
Total deferred liabilities	<u>\$ 4,044</u>	<u>\$ 11,696</u>	<u>\$ (8,872)</u>	<u>\$ 6,868</u>

11. Leases

We have entered into various long-term non-cancelable lease arrangements for our facilities and equipment expiring at various times through 2042. Certain of these arrangements have free rent periods or escalating rent payment provisions, which we recognize lease cost under such arrangements on a straight-line basis over the life of the leases. We have two campuses in Massachusetts, our Cambridge campus and our Moderna Technology Center (MTC), located in Norwood. We also lease other office and lab spaces globally for our business operations.

Operating Leases***Cambridge Campus***

We occupy a multi-building campus at Technology Square in Cambridge, Massachusetts with a mix of offices and research laboratory space totaling approximately 261,000 square feet. Our Cambridge campus leases have expiry ranges from 2024 to 2029.

In August 2019, we entered into an amendment to our lease agreements to consolidate our Technology Square space in Cambridge, Massachusetts. This included entering into a forward-starting lease agreement starting in January 2020 to acquire approximately 50,000 square feet of additional space at 200 Technology Square. In addition, our existing 200 Technology Square lease was extended for two years to 2029. As part of the lease amendment, we completely exited our leased space of approximately 60,000 square feet at 500 Technology Square by May 2020. We are also investing in a new Moderna Science Center (MSC) in Cambridge, to create a purpose-built space to support our next chapter of discovery (see Note 12). In connection with our MSC investment, in September 2021, we entered into an amendment to our lease agreements to allow for an option for early termination of the leases, either in part or full. Notification of the intent to exercise the option must be provided by August 2023. We have not elected to exercise this option.

We record operating lease cost for each of our operating leases on a straight-line basis from lease commencement date through the end of the lease term. Operating lease cost is recorded in operating expenses in our consolidated statements of operations.

Finance Leases***Moderna Technology Center***

We have an industrial technology center in Norwood, Massachusetts, our Moderna Technology Center (MTC), which comprises three buildings, MTC South, MTC North, and MTC East.

In August 2016, we entered into a lease agreement for approximately 200,000 square feet of office, laboratory, and light manufacturing space (MTC South). The lease had an initial expiration of September 2032 with the option to extend the term for two extension periods of ten years each at market-based rents.

In February 2019, we entered into a lease agreement for office and laboratory space of approximately 200,000 square feet (MTC North). The lease commenced in the second quarter of 2019 and had an initial expiration date of 2031 with the option to extend the lease for up to four additional five-year terms. In May 2020, we entered into an amendment to the lease whereby we exercised an option available in the original lease to receive a tenant improvement allowance in the amount of \$22 million to be paid back over the term of the lease with interest and extend the term of the lease to 2035.

In April 2021, we entered into a lease agreement for a 240,000 square foot building for expansion of our commercial and clinical activities (MTC East). The lease had an initial expiration date of February 2034 with the option to extend the term for two extension periods of five years each at market-based rents.

In December 2021, we entered into an omnibus amendment to extend the lease terms of our three MTC leases to 2042. We have the option to extend the term for three extension periods of five years. The base rent is subject to increases over the term of the lease.

Embedded Leases

We have entered into multiple contract manufacturing service agreements with third parties which contain embedded leases within the scope of ASC 842. As of December 31, 2021 and 2020, we had lease liabilities of \$166 million and \$24 million, respectively, related to the embedded leases. Certain embedded leases dedicated to our COVID-19 vaccine program prior to the EUA from the FDA were deemed to have no alternative use. The related right-of-use assets of \$62 million were charged to research and development expense for the year ended December 31, 2020.

Operating and financing lease right-of-use assets and lease liabilities as of December 31, 2021 and 2020 were as follows (in millions):

	December 31,	
	2021	2020
Assets:		
Right-of-use assets, operating, net ^{(1) (2)}	\$ 142	\$ 90
Right-of-use assets, financing, net ^{(3) (4)}	665	55
Total	\$ 807	\$ 145
Liabilities:		
Current:		
Operating lease liabilities ⁽⁵⁾	\$ 46	\$ 6
Financing lease liabilities ⁽⁵⁾	165	24
Total current lease liabilities	211	30
Non-current:		
Operating lease liabilities, non-current	106	97
Financing lease liabilities, non-current	599	110
Total non-current lease liabilities	705	207
Total	\$ 916	\$ 237

⁽¹⁾ These assets are real estate related assets, which include land, office and laboratory spaces.

⁽²⁾ Net of accumulated amortization.

⁽³⁾ These assets are real estate assets related to the MTC leases as well as assets related to contract manufacturing service agreements.

⁽⁴⁾ Included in property and equipment in the consolidated balance sheets, net of accumulated depreciation.

⁽⁵⁾ Included in other current liabilities in the consolidated balance sheets.

The components of the lease costs for the years ended December 31, 2021 and 2020 were as follows (in millions):

	December 31,	
	2021	2020
Operating lease costs	\$ 24	\$ 17
Financing lease costs:		
Amortization of right-of-use assets, financing leases	189	1
Interest expense for financing lease liabilities	17	10
Total financing lease costs	\$ 206	\$ 11
Short term lease costs	\$ 49	\$ 13
Variable lease costs	\$ 100	\$ 5

Supplemental cash flow information relating to our leases for the years ended December 31, 2021 and 2020 was as follows (in millions):

	December 31,	
	2021	2020
Cash paid for amounts included in measurement of lease liabilities:		
Operating cash flows used in operating leases	\$ (19)	\$ (15)
Operating cash flows used in financing leases	(14)	(9)
Financing cash flows used in financing leases	(140)	(8)
Operating lease non-cash items:		
Changes in right-of-use assets related to lease modifications and reassessments	\$ (7)	\$ 7
Right-of-use assets obtained in exchange for operating lease liabilities	72	17
Finance lease non-cash items:		
Changes in right-of-use assets related to lease modifications and reassessments	\$ 674	\$ 46
Right-of-use assets obtained in exchange for financing lease liabilities	126	—
Changes in financing lease liabilities	3	1

Weighted average remaining lease terms and discount rates as of December 31, 2021 were as follows:

	December 31,
	2021
Remaining lease term:	
Operating leases	5 years
Finance leases	28 years
Discount rate:	
Operating leases	6.8 %
Finance leases	3.1 %

Future minimum lease payments under non-cancelable lease agreements as of December 31, 2021, were as follows (in millions):

Fiscal Year	Operating Leases	Financing Leases ⁽¹⁾
2022	\$ 54	\$ 184
2023	39	20
2024	15	20
2025	16	20
2026	16	21
Thereafter	51	1,058
Total minimum lease payments	191	1,323
Less amounts representing interest	(39)	(559)
Present value of lease liabilities	\$ 152	\$ 764

⁽¹⁾ Include the optional extensions in the MTC lease terms which represent a total of \$637 million undiscounted future lease payments.

12. Commitments and Contingencies

Legal Proceedings

We are not currently a party to any material legal proceedings.

Indemnification Obligations

As permitted under Delaware law, we indemnify our officers, directors, and employees for certain events, occurrences while the officer, or director is, or was, serving at our request in such capacity. The term of the indemnification is for the officer's or director's lifetime.

We have standard indemnification arrangements in our leases for laboratory and office space that require us to indemnify the landlord against any liability for injury, loss, accident, or damage from any claims, actions, proceedings, or costs resulting from certain acts, breaches, violations, or non-performance under our leases.

We enter into indemnification provisions under our agreements with counterparties in the ordinary course of business, typically with business partners, contractors, clinical sites and customers. Under these provisions, we generally indemnify and hold harmless the indemnified party for losses suffered or incurred by the indemnified party as a result of our activities. These indemnification provisions generally survive termination of the underlying agreement. The maximum potential amount of future payments we could be required to make under these indemnification provisions is unlimited.

Through December 31, 2021 and 2020, we had not experienced any losses related to these indemnification obligations, and no material claims were outstanding. We do not expect significant claims related to these indemnification obligations and, consequently, concluded that the fair value of these obligations is negligible, and no related reserves were established.

Purchase Commitments and Purchase Orders

We enter into agreements in the normal course of business with vendors and contract manufacturing organizations (CMOs) for raw materials and manufacturing services and with vendors for preclinical research studies, clinical trials and other goods or services. As of December 31, 2021, we had \$2.5 billion of non-cancelable purchase commitments related to raw materials and manufacturing agreements, which are expected to be paid through 2025. As of December 31, 2021, we had \$89 million of non-cancelable purchase commitments related to clinical services and other goods and services which are expected to be paid through 2026. These amounts represent our minimum contractual obligations, including termination fees.

In addition to purchase commitments, we have agreements with third parties for various services, including services related to clinical operations and support and contract manufacturing, for which we are not contractually able to terminate for convenience and avoid any and all future obligations to the vendors. Certain agreements provide for termination rights subject to termination fees or wind down costs. Under such agreements, we are contractually obligated to make certain payments to vendors, mainly, to reimburse them for their unrecoverable outlays incurred prior to cancellation. At December 31, 2021, we had cancelable open purchase orders of \$2.4 billion in total under such agreements for our significant clinical operations and support and contract manufacturing. These amounts represent only our estimate of those items for which we had a contractual commitment to pay at December 31, 2021, assuming we would not cancel these agreements. The actual amounts we pay in the future to the vendors under such agreements may differ from the purchase order amounts.

Licenses to Patented Technology

On June 26, 2017, we entered into sublicense agreements with Cellscript, LLC and its affiliate, mRNA RiboTherapeutics, Inc. to sublicense certain patent rights. Pursuant to each agreement, we are required to pay certain license fees, annual maintenance fees, minimum royalties on future net sales and milestone payments contingent on achievement of certain development, regulatory and commercial milestones for specified products, on a product-by-product basis. Commercial milestone payments, up to \$24 million, and royalties based on annual net sales of licensed products for therapeutic and prophylactic products are accounted for as additional expense of the related product sales in the period in which the corresponding sales occur. In 2021 and 2020, we recognized \$641 million and \$7 million, respectively, of royalties and commercial milestone payments associated with our product sales, which was recorded to cost of sales in our consolidated statements of operations. We did not recognize any such royalties and payments in 2019.

Additionally, we have other in-license agreements with third parties which require us to make future development, regulatory and commercial milestone payments for specified products associated with the agreements. The achievement of these milestones was not deemed probable as of December 31, 2021.

Moderna Science Center

In September 2021, we announced an investment in the development of the MSC in Cambridge, Massachusetts. The MSC is expected to integrate scientific and non-scientific spaces, including our principal executive offices, and will be built to support our growth as we continue to advance our pipeline of mRNA medicines. In relation to the investment, we entered into a lease agreement for approximately 462,000 square feet and will undergo an approximately two-year building project. Following completion of the building project, the lease term is 15 years, subject to our right to extend the lease for up to two additional seven-year terms. Pursuant to this lease agreement, we are committed to approximately \$1.1 billion non-cancellable rent payments for the initial lease term. We expect to begin a phased move-in process in 2023.

13. Stockholders' Equity

On February 14, 2020, we sold 26,315,790 shares of common stock at a price of \$19.00 per share through a public equity offering. The aggregate net proceeds from the offering were \$478 million, net of underwriting discounts, commissions and offering expenses. In addition, the underwriters exercised their options to purchase an additional 3,947,368 shares of common stock at the public offering price less underwriting discounts, resulting in additional net proceeds of \$72 million.

On May 21, 2020, we sold 17,600,000 shares of common stock at a price of \$76.00 per share through a public equity offering. The aggregate net proceeds from the offering were \$1.3 billion, net of underwriting discounts, commissions and offering expenses.

14. Stock-Based Compensation

Equity Plans

In August 2016, we adopted the 2016 Stock Option and Grant Plan (the 2016 Equity Plan), which replaced the 2013 Option Plan and the 2013 Incentive Plan. The 2016 Equity Plan provided for the grant of incentive stock options, non-qualified stock options, restricted stock, unrestricted stock, and restricted stock units to our employees, officers, directors, consultants, and other key persons.

In connection with our initial public offering (IPO), we adopted the 2018 Stock Option and Incentive Plan (the 2018 Equity Plan) in November 2018. The 2018 Equity Plan became effective on the date immediately prior to the effective date of the IPO and replaced our 2016 Plan. The 2018 Equity Plan provides flexibility to our compensation committee to use various equity-based incentive awards as compensation tools to motivate our workforce. The 2018 Equity Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 4% of the outstanding number of shares of our common stock on the immediately preceding December 31, or such lesser number of shares as determined by the Compensation and Talent Committee of our Board of Directors. The Compensation and Talent Committee chose not to increase the number of shares available under the 2018 Plan on January 1, 2021 or January 1, 2022. The shares of common stock underlying any awards that are forfeited, canceled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by us prior to vesting, satisfied without any issuance of stock, expire or are otherwise terminated (other than by exercise) under the 2018 Equity Plan and the 2016 Plan will be added back to the shares of common stock available for issuance under the 2018 Equity Plan.

The terms and conditions of stock-based awards are defined at the sole discretion of our Board of Directors. We issue service-based awards, vesting over a defined period of service, and performance-based awards, vesting upon achievement of defined conditions. Service based awards generally vest over a four-year period, with the first 25% of such awards vesting following twelve months of continued employment or service. The remaining awards vest in twelve quarterly installments over the following twelve quarters. Stock options granted under the 2018 Equity Plan and the 2016 Equity Plan expire ten years from the date of grant and the exercise price must be at least equal to the fair market value of common stock on the grant date.

As of December 31, 2021, we had a total of 57 million shares reserved for future issuance under our Equity Plans, of which 30 million shares were reserved for equity awards previously granted, and 27 million shares were available for future grants under the 2018 Equity Plan. No additional awards will be granted under the 2016 Equity Plan as it was replaced by the 2018 Equity Plan.

Options

We have granted options generally through the 2018 Equity Plan and 2016 Equity Plan. The following table summarizes our option activity as of December 31, 2021 and 2020:

	Number of Options (in millions)	Weighted Average Exercise Price per Share	Weighted- Average Remaining Contractual Term	Aggregate Intrinsic Value ⁽¹⁾ (in millions)
Outstanding at December 31, 2020	34.06	\$ 17.14	6.7 years	\$ 2,976
Granted	1.48	209.41		
Exercised	(7.07)	15.84		
Canceled/forfeited	(1.06)	37.46		
Outstanding at December 31, 2021	27.41	27.08	5.8 years	6,247
Exercisable at December 31, 2021	17.33	13.23	4.9 years	4,173
Expected to vest at December 31, 2021	10.08	50.94	7.5 years	2,074

⁽¹⁾ Aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the fair value of common stock for those options in the money as of December 31, 2021.

The total intrinsic value of options exercised was \$1.6 billion, \$786 million, and \$76 million for the years ended December 31, 2021, 2020, and 2019, respectively. The aggregate intrinsic value represents the difference between the exercise price and the selling price received by option holders upon the exercise of stock options during the period. The excess tax benefits realized from tax deductions from option exercises were \$325 million during the year ended December 31, 2021. For the years ended December 31, 2020 and 2019, there were no excess tax benefits realized from tax deductions from option exercises due to cumulative losses and valuation allowances. The total consideration recorded as a result of stock option exercises was approximately \$112 million, \$179 million, and \$48 million for the years ended December 31, 2021, 2020, and 2019.

Restricted Common Stock Units (RSUs) and Performance Stock Units (PSUs)

We have granted RSUs and PSUs generally through the 2018 Equity Plan. The following table summarizes our RSU and PSU activity during the year ended December 31, 2021:

	Number of Units (in millions)	Weighted Average Grant Date Fair Value per Unit
Outstanding, non-vested at December 31, 2020	2.19	\$ 30.85
Issued	0.71	210.33
Vested	(0.60)	29.29
Canceled/forfeited	(0.16)	63.72
Outstanding, non-vested at December 31, 2021	2.14	88.55

The total fair value of RSUs and PSUs vested during the years ended December 31, 2021, 2020, and 2019, was \$18 million, \$5 million, and \$5 million, respectively. The total intrinsic value of RSUs and PSUs vested during the years ended December 31, 2021, 2020, and 2019, was \$141 million, \$14 million and \$12 million, respectively.

During the first quarter of 2021, we granted an immaterial amount of PSUs to certain senior executives with vesting that is contingent upon the achievement of specified preestablished goals over the performance period, generally three years. The actual number of common shares ultimately issued is calculated by multiplying the number of PSUs by a payout percentage ranging from 0% to 200%. The estimated fair value of PSUs is based on the grant date fair value.

2018 Employee Stock Purchase Plan

In November 2018, we adopted the 2018 Employee Stock Purchase Plan (ESPP), which became effective on December 5, 2018. We will make one or more offerings, consisting of one or more purchase periods, each year to our eligible employees to purchase shares under the ESPP. Offerings will usually begin every six months and will continue for six-month periods, referred to as offering periods.

The purchase price at which shares are sold under the ESPP will be equal to 85% of the lower of the fair market value of the shares on the first business day of the offering period or the last business day of the purchase period. Employees are generally eligible to participate through payroll deductions of between 1% to 50% of their compensation and may not purchase more than 3,000 shares of common stock during each purchase period or \$25,000 worth of shares of common stock in any calendar year. We began our first ESPP offering on June 1, 2019. There were 81,423, 251,752, and 171,343 shares of common stock sold at a weighted average price of \$145.90, \$27.97, and \$16.87 per share under the ESPP during the years ended December 31, 2021, 2020, and 2019, respectively. As of December 31, 2021, 4 million shares were available for future issuance under the ESPP.

Valuation and Stock-Based Compensation Expense

Stock-based compensation for options granted under our Equity Plans and share purchases under our ESPP is determined using the Black-Scholes option pricing model. The weighted-average assumptions used to estimate the fair value of options granted and ESPP for the years ended December 31, 2021, 2020, and 2019 were as follows:

	Weighted Average Years Ended December 31,		
	2021	2020	2019
Options:			
Risk-free interest rate	0.84 %	0.83 %	2.29 %
Expected term	6.10 years	6.11 years	6.07 years
Expected volatility	46 %	58 %	61 %
Expected dividends	— %	— %	— %
Weighted average fair value per share	\$ 91.84	\$ 19.30	\$ 11.35
ESPP:			
Risk-free interest rate	0.08 %	0.14 %	1.95 %
Expected term	0.50 years	0.50 years	0.50 years
Expected volatility	34 %	54 %	53 %
Expected dividends	— %	— %	— %
Weighted average fair value per share	\$ 64.25	\$ 32.18	\$ 5.98

Stock-Based Compensation Expense

The following table presents the components and classification of stock-based compensation expense for the years ended December 31, 2021, 2020, and 2019 (in millions):

	Years Ended December 31,		
	2021	2020	2019
Options	\$ 96	\$ 78	\$ 75
RSUs and PSUs	42	12	5
ESPP	4	3	1
Total	\$ 142	\$ 93	\$ 81
Cost of sales	\$ 22	\$ —	\$ —
Research and development	68	56	48
Selling, general and administrative	52	37	33
Total	\$ 142	\$ 93	\$ 81

For the years ended December 31, 2021, 2020, and 2019, we recognized stock-based compensation expense of \$16 million, \$10 million, and \$10 million, respectively, related to performance-based awards, including awards with vesting or commencement contingent upon our IPO. Stock-based compensation expenses related to non-employee awards were immaterial for the years ended December 31, 2021, 2020, and 2019.

As of December 31, 2021, there were \$349 million of total unrecognized compensation cost related to non-vested stock-based compensation with respect to options, RSUs and PSUs granted. That cost is expected to be recognized over a weighted-average period of 2.9 years at December 31, 2021.

Share Repurchase Program

On August 2, 2021, our Board of Directors authorized a Share Repurchase Program (2021 Repurchase Program) of our common stock, with an expiration date no later than August 2, 2023. Pursuant to the 2021 Repurchase Program, we may repurchase up to \$1.0 billion of our outstanding common stock. The timing and actual number of shares repurchased depend on a variety of factors, including price, general business and market conditions, and other investment opportunities, and shares may be repurchased through open market purchases through the use of trading plans intended to qualify under Rule 10b5-1 under the Securities Exchange Act of 1934, as amended (the Exchange Act).

In the fourth quarter of 2021, we repurchased 3.5 million shares of our common stock under the 2021 Repurchase Program for an aggregate of \$857 million, including commissions and fees. As of December 31, 2021, there was a total of \$143 million remaining for repurchases of our common stock under the 2021 Repurchase Program.

15. Employee Benefit Plans

We provide a retirement savings option to our eligible U.S. employees through the Moderna, Inc. 401(k) Plan (the 401(k) Plan), subject to certain limitations. As allowed under Section 401(k) of the Internal Revenue Code, the 401(k) Plan allows tax deferred salary deductions for eligible employees. We match 50% up to the first 6% contributed by a participant. All matching contributions are immediately vested. Total matching contributions to the 401(k) Plan were \$18 million, \$5 million, and \$4 million for the years ended December 31, 2021, 2020, and 2019, respectively.

We maintain various defined benefit plans to provide termination and postretirement benefits to certain eligible employees outside of the U.S. The unfunded benefit plan obligations were \$9 million as of December 31, 2021, which is recognized in other long-term liabilities in our consolidated balance sheets.

16. Income Taxes

Income (loss) before income taxes for the years ended December 31, 2021, 2020, and 2019 consisted of the following (in millions):

	Years Ended December 31,		
	2021	2020	2019
United States	\$ 13,108	\$ (745)	\$ (509)
Foreign	177	1	(6)
Income (loss) before income taxes	<u>\$ 13,285</u>	<u>\$ (744)</u>	<u>\$ (515)</u>

The provision for (benefit from) income taxes for the years ended December 31, 2021, 2020, and 2019 consisted of the following components (in millions):

	Years Ended December 31,		
	2021	2020	2019
Current:			
Federal	\$ 1,304	\$ —	\$ —
State	35	—	—
Foreign	40	3	—
Total current	<u>\$ 1,379</u>	<u>\$ 3</u>	<u>\$ —</u>
Deferred:			
Federal	\$ (288)	\$ —	\$ (1)
State	(6)	—	—
Foreign	(2)	—	—
Total deferred	<u>(296)</u>	<u>—</u>	<u>(1)</u>
Total provision for (benefit from) income taxes	<u>\$ 1,083</u>	<u>\$ 3</u>	<u>\$ (1)</u>

The reconciliation of the federal statutory income tax rate to our effective tax rate for the years ended December 31, 2021, 2020, and 2019 was as follows:

	Years Ended December 31,		
	2021	2020	2019
Federal statutory tax rate	21.0 %	21.0 %	21.0 %
Change in valuation allowance	(5.4)%	(47.4)%	(33.0)%
Foreign-derived intangible income	(4.8)%	— %	(0.2)%
Stock-based compensation	(2.6)%	19.8 %	— %
Federal research and development credits	(0.7)%	3.8 %	2.5 %
State taxes, net of federal benefits	0.5 %	3.6 %	7.9 %
Non-deductible items	— %	(0.8)%	1.6 %
Other	0.1 %	(0.3)%	0.2 %
Effective tax rate	8.1 %	(0.3)%	— %

We are subject to U.S. federal, state, and foreign income taxes. Our effective tax rate for the year ended December 31, 2021 was 8.1% and was lower than the federal statutory tax rate primarily due to the tax benefits related to the release of the valuation allowance on most of our deferred tax assets, foreign-derived intangible income deduction and stock-based compensation. Our effective tax rate for the years ended December 31, 2020 and December 31, 2019 was lower than the federal statutory tax rate primarily due to the valuation allowance on our deferred tax assets.

Deferred income taxes reflect the tax effect of temporary differences between the carrying amount of assets and liabilities for financial reporting and the amounts used for income tax purposes, tax credit carryforwards and the tax effect of net operating loss carryforwards. Significant components of our deferred tax assets and tax liabilities as of December 31, 2021 and 2020 were as follows (in millions):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	\$ 69	\$ 587
Stock-based compensation	44	33
Capitalized licenses, research and development and start-up costs	204	14
Tax credit carryforwards	80	99
Deferred revenue	43	30
Operating lease liabilities	32	22
Financing lease liabilities	136	24
Other	67	65
Total deferred tax assets	675	874
Less: valuation allowance	(149)	(823)
Net deferred tax assets	\$ 526	\$ 51
Deferred tax liabilities:		
Right-of-use assets, financing	\$ (119)	\$ (12)
Right-of-use assets, operating	(31)	(20)
Property and equipment	(49)	(18)
Other	(1)	(1)
Total deferred tax liabilities	(200)	(51)
Net deferred tax assets	\$ 326	\$ —

On a quarterly basis, we reassess the valuation allowance on our deferred tax assets, weighing positive and negative evidence to assess the realizability of the deferred tax assets. In the first quarter of 2021, we reassessed the valuation allowance noting the increase in positive evidence, including significant revenue growth, expectations regarding future profitability, and successful supply chain and

manufacturing capabilities to meet global product demand. After assessing both the positive evidence and negative evidence, we determined it was more likely than not that we will realize the majority of our deferred tax assets, and we released the valuation allowance on the majority of our deferred tax assets, accordingly. We continue to maintain a valuation allowance on certain state deferred tax assets.

Changes in the valuation allowance for deferred tax assets during the year ended December 31, 2021 primarily related to the release of the valuation allowance on deferred tax assets. The changes during the years ended December 31, 2020 and 2019 primarily related to the increase in valuation allowance on net operating loss carryforwards and research and development tax credit carryforwards. The changes were as follows (in millions):

	Years Ended December 31,		
	2021	2020	2019
Valuation allowance at beginning of the period	\$ 823	\$ 471	\$ 308
Decreases recorded as benefit to income tax provision	(722)	—	—
Increases to valuation allowance	48	352	163
Valuation allowance at December 31	<u>\$ 149</u>	<u>\$ 823</u>	<u>\$ 471</u>

At December 31, 2021, we had \$1.0 billion of state net operating loss carryforwards, which begin to expire in 2032. At December 31, 2021, we also had state tax credit carryforwards of \$102 million, the majority of which will begin to expire in 2030.

We file U.S. federal income tax returns and income tax returns in various state, local and foreign jurisdictions. All tax years since date of incorporation remain open to examination by the major taxing jurisdictions (federal and state) to which we are subject, as carryforward attributes generated in past years may still be adjusted upon examination by the Internal Revenue Service or the state authorities if they have or will be used in a future period. There are no open tax examinations at this time.

We recognize, in our financial statements, the effect of a tax position when it is more likely than not, based on the technical merits, that the position will be sustained upon examination. A reconciliation of the beginning and ending amounts of unrecognized tax benefits during the years ended December 31, 2021, 2020, and 2019 were as follows (in millions):

	Years Ended December 31,		
	2021	2020	2019
Unrecognized tax benefits at beginning of the period	\$ —	\$ —	\$ —
Additions based on tax positions for current year	54	—	—
Additions based on tax positions for prior years	14	—	—
Unrecognized tax benefits at end of the period	<u>\$ 68</u>	<u>\$ —</u>	<u>\$ —</u>

As of December 31, 2021, we had \$43 million of net unrecognized tax benefits, which would affect our tax rate if recognized. Unrecognized tax benefits may change during the next twelve months for items that arise in the ordinary course of business. We do not anticipate a material change to our unrecognized tax benefits over the next twelve months that would have an adverse effect on our consolidated operating results. We recognize interest and penalties, if applicable, related to uncertain tax positions as a component of income tax expense; however, there has been no interest or penalties accrued to date.

17. Earnings (Loss) per Share

The computation of basic earnings (loss) per share (EPS) is based on the weighted-average number of our common shares outstanding. The computation of diluted EPS is based on the weighted-average number of our common shares outstanding and potential dilutive common shares outstanding during the period as determined by using the treasury stock method.

Basic and diluted EPS for the years ended December 31, 2021, 2020 and 2019 were calculated as follows (in millions, except per share data):

	Years Ended December 31,		
	2021	2020	2019
Numerator:			
Net income (loss)	\$ 12,202	\$ (747)	\$ (514)
Denominator:			
Basic weighted-average common shares outstanding	403	381	331
Effect of dilutive securities	28	—	—
Diluted weighted-average common shares outstanding	431	381	331
Basic EPS	\$ 30.31	\$ (1.96)	\$ (1.55)
Diluted EPS	\$ 28.29	\$ (1.96)	\$ (1.55)

The following common stock equivalents, presented based on amounts outstanding as of December 31, 2021, 2020 and 2019, were excluded from the calculation of diluted net income (loss) per share attributable to common stockholders for the periods indicated because their inclusion would have been anti-dilutive (in millions):

	December 31,		
	2021	2020	2019
Stock options	1	34	46
Restricted common stock units	—	2	1
Total	1	36	47

18. Geographic Information

Geographic Revenue

We operate in one reporting segment that primarily focuses on the discovery, development and commercialization of mRNA medicines. Our chief executive officer manages our operations and evaluates our financial performance on a consolidated basis. Most of our principal operations, other than manufacturing, and our decision-making functions are located at our corporate headquarters in the United States.

Total revenue by geographic area of our customers and collaboration partners was as follows (in millions):

	Years Ended December 31,		
	2021	2020	2019
United States	\$ 6,177	\$ 764	\$ 55
Europe	6,846	33	5
Rest of world ⁽¹⁾	5,448	6	—
Total	\$ 18,471	\$ 803	\$ 60

⁽¹⁾ Includes product sales recognized under the agreement with Gavi (on behalf of the COVAX Facility) as Gavi facilitates a fair allocation and distribution of our COVID-19 vaccine around the world.

Our property and equipment, including financing right-of-use assets, by geographic area was as follows (in millions):

	December 31, 2021
United States	\$ 1,050
Europe	181
Rest of world	10
Total	\$ 1,241

Our property and equipment, including financing right-of-use assets, was principally located within the United States as of December 31, 2020.

19. Subsequent Events

In January 2022, we repurchased an additional 0.6 million shares of our common stock under the 2021 Repurchase Program for an aggregate of \$143 million including commissions and fees. We have repurchased the entire \$1.0 billion of common stock that was authorized under the 2021 Repurchase Program.

On February 22, 2022, our Board of Directors authorized a new Share Repurchase Program (2022 Repurchase Program) of our common stock, with no expiration date. Pursuant to the 2022 Repurchase Program, we may repurchase up to \$3.0 billion of our outstanding common stock. The timing and actual number of shares repurchased will depend on a variety of factors, including price, general business and market conditions, and other investment opportunities, and shares may be repurchased through open market purchases through the use of trading plans intended to qualify under Rule 10b5-1 under the Exchange Act.

Subsequent to December 31, 2021, we have entered into several supply agreements with customers to provide our COVID-19 vaccine, up to 66 million doses, and have received upfront deposits of \$210 million, based on the initial confirmed volume, subject to modifications.

Subsequent to December 31, 2021, we have entered binding purchase commitments with third-party contractual manufacturing organizations for dedicated facilities and fill & finish services for our COVID-19 vaccine. We are currently committed to minimum non-cancelable purchase obligations of \$1.9 billion related to these agreements, of which \$213 million is expected to be paid within 2022 and the remaining is expected to be paid through 2029.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2021, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management’s Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as such term is defined in Exchange Act Rule 13a-15(f)) to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Management assessed our internal control over financial reporting as of December 31, 2021. Management based its assessment on criteria established in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework). Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2021.

The effectiveness of our internal control over financial reporting as of December 31, 2021 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report included in this Annual Report on Form 10-K.

Changes in Internal Controls over Financial Reporting

During the three months ended December 31, 2021, there were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act), which have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations on the Effectiveness of Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, believe that our disclosure controls and procedures and internal control over financial reporting are designed to provide reasonable assurance of achieving their objectives and are effective at the reasonable assurance level. However, our management does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all errors and all fraud. A control system, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, have been detected. These inherent limitations include the realities that judgments in decision making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by the collusion of two or more people or by a management override of the controls. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Moderna, Inc.

Opinion on the Internal Control Over Financial Reporting

We have audited Moderna, Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Moderna, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and December 31, 2020, the related consolidated statements of operations, comprehensive income (loss), stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes and our report dated February 25, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2022

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

None Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2022 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 11. Executive Compensation

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2022 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2022 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2022 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 14. Principal Accounting Fees and Services

Our independent public accounting firm is Ernst & Young LLP, Boston, Massachusetts, PCAOB Auditor ID 00042.

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2022 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) Documents filed as part of this report.

(1) Financial statements.

For a list of the consolidated financial statements included herein, see “Index to Consolidated Financial Statements” under Part I, Item 8 of this Annual Report on Form 10-K.

(2) Schedules.

No financial statement schedules have been submitted because they are not required or are not applicable or because the information required is included in the consolidated financial statements or the notes thereto.

(3) Exhibits.

Exhibit No.	Exhibit Index
3.1	Amended and Restated Certificate of Incorporation of the Registrant. (2)
3.2	Amended and Restated By-laws of the Registrant. (2)
4.1	Specimen Common Stock Certificate. (1)
4.2	Second Amended and Restated Investors’ Rights Agreement by and among the Registrant and certain of its stockholders, dated May 7, 2018. (1)
4.3	Description of Capital Stock. (10)
10.1#	2016 Stock Option and Grant Plan, as amended, and forms of award agreements thereunder. (1)
10.2#	2018 Stock Option and Incentive Plan and forms of award agreements thereunder. (1)
10.3#	Form of Indemnification Agreement between the Registrant and each of its directors. (1)
10.4†	Master Collaboration and License Agreement, by and between Moderna Therapeutics, Inc. and Merck Sharp & Dohme Corp., dated as of January 12, 2015, as amended by Amendment No. 1 dated as of January 8, 2016, Amendment No. 2 dated as of June 28, 2016, Amendment No. 3 dated as of June 28, 2016 and Amendment No. 4 dated as of June 28, 2016. (1)
10.5†	Amended and Restated mRNA Cancer Vaccine Collaboration and License Agreement, by and between ModernaTX, Inc. and Merck Sharp & Dohme Corp., dated as of April 17, 2018. (1)
10.6†	Amended and Restated Option Agreement by and between ModernaTX, Inc. and AstraZeneca AB, dated as of June 15, 2018. (1)
10.7†	Amended and Restated Services and Collaboration Agreement by and between ModernaTX, Inc. and AstraZeneca AB, dated as of June 15, 2018. (1)
10.8†	Patent Sublicense Agreement, by and among ModernaTX, Inc. and Cellscript, LLC and mRNA RiboTherapeutics, Inc. (solely with respect to certain provisions), dated as of June 26, 2017. (1)
10.9	Lease Agreement, by and between Moderna Therapeutics, Inc. and ARE-Tech Square, LLC, dated as of May 26, 2016, as amended by Amendment No. 1 dated as of August 31, 2016, Amendment No. 2 dated as of December 31, 2016, Amendment No. 3 dated as of April 24, 2017, Amendment No. 4 dated as of April 13, 2018. (1)
10.10	Fifth Amendment to Lease Agreement, by and between ModernaTX, Inc. and ARE-Tech Square, LLC, dated as of August 28, 2019. (3)
10.11	Net Lease by and between Moderna Therapeutics, Inc. and Campanelli-TriGate Norwood Upland, LLC, dated as of August 29, 2016, as amended by Amendment No. 1 dated as of April 10, 2017 and Amendment No. 2 dated as of March 16, 2018. (1)
10.12*	Third Amendment, dated September 11, 2018, Fourth Amendment, dated March 28, 2019, and Omnibus Amendment, dated December 30, 2021, to Net Lease, dated as of August 29, 2016, as amended.
10.13#	Amended and Restated Executive Severance Plan and Form of Participation Letter, as amended on November 4, 2018. (1)
10.14#	Letter Agreement by and between the Company and Stéphane Bancel, dated as of June 13, 2018, as amended by Amendment No. 1 dated as of November 4, 2018. (1)
10.15#	Letter Agreement by and between the Company and Stephen Hoge, dated as of October 17, 2017. (1)
10.16#*	Offer Letter by and between ModernaTX, Inc. and Corinne Le Goff, dated as of December 28, 2020.

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10.17#*	<u>Executive Separation and Transitional Services Agreement by and between ModernaTX, Inc. and Corinne Le Goff, dated as of November 11, 2021.</u>
10.18#*	<u>Consulting Agreement by and between ModernaTX, Inc. and Corinne Le Goff, effective as of December 17, 2021.</u>
10.19#*	<u>Employment Letter Agreement between ModernaTX, Inc. and Shannon Klinger, dated as of March 4, 2021.</u>
10.20#	<u>Senior Executive Cash Incentive Bonus Plan. (1)</u>
10.21#	<u>Amended and Restated Non-Employee Director Compensation Policy. (4)</u>
10.22#	<u>Form of Indemnification Agreement between the Registrant and each of its officers. (1)</u>
10.23#	<u>2018 Employee Stock Purchase Plan. (1)</u>
10.24#*	<u>Form of Employee Restricted Stock Unit Award Agreement.</u>
10.25#*	<u>Form of Employee Non-Qualified Stock Option Agreement.</u>
10.26#*	<u>Form of Non-Employee Director Restricted Stock Unit Award Agreement.</u>
10.27#*	<u>Form of Non-Employee Director Non-Qualified Stock Option Agreement.</u>
10.28#	<u>Form of Performance-Based Restricted Stock Unit Award Agreement under the 2018 Stock Option and Incentive Plan. (4)</u>
10.29†	<u>Agreement No. HHSO100201600029C, by and between the Company and the Biomedical Advanced Research and Development Authority, dated as of April 16, 2020, as amended on May 24, 2020, June 16, 2020, July 25, 2020, August 31, 2020 and September 15, 2020. (5)</u>
10.30†	<u>Amendment No. 6, dated February 16, 2021, to Agreement No. HHSO100201600029C, by and between ModernaTX, Inc. and the Biomedical Advanced Research and Development Authority, dated as of April 16, 2020. (4)</u>
10.31†	<u>Amendment No. 7, dated March 12, 2021, to Agreement No. HHSO100201600029C, by and between ModernaTX, Inc. and the Biomedical Advanced Research and Development Authority, dated as of April 16, 2020. (4)</u>
10.32†	<u>Amendment Nos. 8 and 9 to Agreement No. HHSO100201600029C, by and between ModernaTX, Inc. and the Biomedical Advanced Research and Development Authority, dated as of April 16, 2020. (8)</u>
10.33†	<u>Amendment No. 10 to Agreement No. HHSO100201600029C, by and between ModernaTX, Inc. and the Biomedical Advanced Research and Development Authority, dated as of April 16, 2020. (9)</u>
10.34†*	<u>Amendment No. 11 to Agreement No. HHSO100201600029C, by and between ModernaTX, Inc. and the Biomedical Advanced Research and Development Authority, dated as of November 4, 2021.</u>
10.35†	<u>Global Long Term Agreement, by and among ModernaTX Inc., Lonza Sales Ltd., and Lonza Ltd., dated September 4, 2020. (6)</u>
10.36†	<u>Award Contract No. W911QY20C0100, by and between Moderna US Inc. and the Army Contracting Command of the U.S. Department of Defense, dated August 9, 2020, as amended September 8, 2020, and September 11, 2020. (6)</u>
10.37†	<u>Amendment No. P00003 to Award Contract No. W911QY20C0100, by and between Moderna US Inc. and the Army Contracting Command of the U.S. Department of Defense, dated December 11, 2020. (7)</u>
10.38†	<u>Amendment Nos. P00004, P00005, P00006, P00007, P00008, P00009, P00010, P00011 and P00012 to Award Contract No. W911QY20C0100, by and between Moderna US Inc. and the Army Contracting Command of the U.S. Department of Defense, dated August 9, 2020. (8)</u>
10.39†	<u>Amendment Nos. P00012, P00013, P00014, P00015, P00016 and P00017 to Award Contract No. W911QY20C0100, by and between Moderna US Inc. and the Army Contracting Command of the U.S. Department of Defense, dated August 9, 2020. (9)</u>
10.40†*	<u>Amendment Nos. P00018, P00019, P00020, and P00021 to Award Contract No. W911QY20C0100, by and between Moderna US Inc. and the Army Contracting Command of the U.S. Department of Defense, dated August 9, 2020.</u>
21.1*	<u>Subsidiaries of the Registrant.</u>
23.1*	<u>Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.</u>
31.1*	<u>Certification of Principal Executive Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>
31.2*	<u>Certification of Principal Financial Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u>
32.1+	<u>Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</u>
32.2+	<u>Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</u>
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document

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101.LAB*	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Link Document
104*	Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101)

* Filed herewith.

† Pursuant to 17 C.F.R. §§230.406 and 230.83, the confidential portions of this exhibit have been omitted and are marked accordingly.

Indicates a management contract or any compensatory plan, contract or arrangement.

+ The certifications furnished in Exhibits 32.1 and 32.2 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

- (1) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-228300) filed with the Securities and Exchange Commission on November 9, 2018.
- (2) Incorporated by reference to the Current Report on Form 8-K (File No. 001-38753) filed with the Securities and Exchange Commission on December 14, 2018.
- (3) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on November 6, 2019.
- (4) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on May 6, 2021.
- (5) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on August 6, 2020.
- (6) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on October 30, 2020.
- (7) Incorporated by reference to the Annual Report on Form 10-K (File No. 001-38753) filed with the Securities and Exchange Commission on February 26, 2021.
- (8) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on August 5, 2021.
- (9) Incorporated by reference to the Quarterly Report on Form 10-Q (File No. 001-38753) filed with the Securities and Exchange Commission on November 4, 2021.
- (10) Incorporated by reference to the Annual Report on Form 10-K (File No. 001-38752) filed with the Securities and Exchange Commission on February 27, 2020.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of the Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

MODERNA, INC.

Date:
February 25, 2022

By: /s/ Stéphane Bancel

Stéphane Bancel
Chief Executive Officer and Director

POWER OF ATTORNEY AND SIGNATURES

Each individual whose signature appears below hereby constitutes and appoints each of Stéphane Bancel and David Meline and as such person's true and lawful attorney-in-fact and agent with full power of substitution and resubstitution, for such person in such person's name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange Commission granting unto each said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as such person might or could do in person, hereby ratifying and confirming all that any said attorney-in-fact and agent, or any substitute or substitutes of any of them, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Stéphane Bancel Stéphane Bancel	Chief Executive Officer and Director (<i>Principal Executive Officer</i>)	February 25, 2022
/s/ David Meline David Meline	Chief Financial Officer (<i>Principal Financial Officer and Principal Accounting Officer</i>)	February 25, 2022
/s/ Noubar B. Afeyan, Ph.D. Noubar B. Afeyan, Ph.D.	Chairman and Director	February 25, 2022
/s/ Stephen Berenson Stephen Berenson	Director	February 25, 2022
/s/ Sandra Horning, M.D. Sandra Horning M.D.	Director	February 25, 2022
/s/ Robert Langer, Sc.D. Robert Langer, Sc.D.	Director	February 25, 2022
/s/ Francois Nader, M.D. Francois Nader M.D.	Director	February 25, 2022
/s/ Elizabeth Nabel, M.D. Elizabeth Nabel, M.D.	Director	February 25, 2022
/s/ Paul Sagan Paul Sagan	Director	February 25, 2022
/s/ Elizabeth Tallett Elizabeth Tallett	Director	February 25, 2022

Exhibit 10.12

THIRD AMENDMENT TO LEASE

THIS THIRD AMENDMENT TO LEASE (this "**Third Amendment**") is made as of September 11, 2018, by and between **ARE-MA REGION NO. 64, LLC**, a Delaware limited liability company ("**Landlord**"), and **MODERNA, INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A. Tenant and Landlord are now parties to that certain Net Lease dated as of August 29, 2016 ("**Original Lease**"), as amended by that certain First Amendment to Lease dated as of April 10, 2017, and as further amended by that certain Second Amendment to Lease dated as March 16, 2018 (as amended, the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises known as 100 Tech Drive, Norwood, Massachusetts (the "**Premises**"). The Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. At Tenant's request, Landlord and Tenant have agreed to amend the Lease as more particularly set forth in this Third Amendment.

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Use of Initial Tenant Work Allowance.** Section 3.1(f) of the Original Lease is hereby amended to provide that the Initial Tenant Work Allowance shall not be available for any work completed (or reimbursement requested) after March 31, 2019.
2. **Brokers.** Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this Third Amendment and that no Broker brought about this transaction. Landlord shall only pay commissions to Broker pursuant to a separate written agreement between Landlord and Broker. Landlord and Tenant each hereby agree to indemnify and hold the other harmless from and against any claims by any Broker, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this Third Amendment.
3. **OFAC.** Tenant and all beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "**OFAC Rules**"), (b) not listed on, and shall not during the term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List or the Sectoral Sanctions Identifications List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.
4. **Miscellaneous.**
 - a. This Third Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions. This Third Amendment may be amended only by an agreement in writing, signed by the parties hereto.

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b. This Third Amendment is binding upon and shall inure to the benefit of the parties hereto, and their respective successors and assigns.

c. This Third Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Third Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this Third Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this Third Amendment. In the event of any conflict between the provisions of this Third Amendment and the provisions of the Lease, the provisions of this Third Amendment shall prevail. Whether or not specifically amended by this Third Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this Third Amendment.

[Signatures are on the next page.]

IN WITNESS WHEREOF, the parties hereto have executed this Third Amendment as of the day and year first above written.

LANDLORD:

ARE-MA REGION NO. 64, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

/s/ Jackie Clem
By: Jackie Clem
Senior Vice President, RE Legal Affairs

TENANT:

MODERNATX, INC.,
a Delaware corporation

By: /s/ Steve Harbin
Its: Norwood Site Head

FOURTH AMENDMENT TO LEASE

THIS FOURTH AMENDMENT TO LEASE (this "**Fourth Amendment**") is made as of March 28, 2019, by and between **ARE-MA REGION NO. 64, LLC**, a Delaware limited liability company ("**Landlord**"), and **MODERNA, INC.**, a Delaware corporation ("**Tenant**").

RECITALS

A. Tenant and Landlord are now parties to that certain Net Lease dated as of August 29, 2016 ("**Original Lease**"), as amended by that certain First Amendment to Lease dated as of April 10, 2017, as further amended by that certain Second Amendment to Lease dated as of March 16, 2018, and as further amended by that certain Third Amendment to Lease dated as of September 11, 2018 (as amended, the "**Lease**"). Pursuant to the Lease, Tenant leases certain premises known as 100 Tech Drive, Norwood, Massachusetts (the "**Premises**"). The Premises are more particularly described in the Lease. Capitalized terms used herein without definition shall have the meanings defined for such terms in the Lease.

B. At Tenant's request, Landlord and Tenant have agreed to amend the Lease as more particularly set forth in this Fourth Amendment.

NOW, THEREFORE, in consideration of the foregoing Recitals, which are incorporated herein by this reference, the mutual promises and conditions contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Use of Initial Tenant Work Allowance.** Section 3.1(f) of the Original Lease is hereby amended to provide that the Initial Tenant Work Allowance shall not be available for any work completed (or reimbursement requested) after September 30, 2019.
2. **Brokers.** Landlord and Tenant each represents and warrants that it has not dealt with any broker, agent or other person (collectively, "**Broker**") in connection with the transaction reflected in this Fourth Amendment and that no Broker brought about this transaction. Landlord shall only pay commissions to Broker pursuant to a separate written agreement between Landlord and Broker. Landlord and Tenant each hereby agree to indemnify and hold the other harmless from and against any claims by any Broker, claiming a commission or other form of compensation by virtue of having dealt with Tenant or Landlord, as applicable, with regard to this Fourth Amendment. . . .
3. **OFAC.** Tenant and all beneficial owners of Tenant are currently (a) in compliance with and shall at all times during the Term of the Lease remain in compliance with the regulations of the Office of Foreign Assets Control ("**OFAC**") of the U.S. Department of Treasury and any statute, executive order, or regulation relating thereto (collectively, the "OFAC Rules"), (b) not listed on, and shall not during the term of the Lease be listed on, the Specially Designated Nationals and Blocked Persons List, Foreign Sanctions Evaders List or the Sectoral Sanctions Identifications List, which are all maintained by OFAC and/or on any other similar list maintained by OFAC or other governmental authority pursuant to any authorizing statute, executive order, or regulation, and (c) not a person or entity with whom a U.S. person is prohibited from conducting business under the OFAC Rules.
4. **Miscellaneous.**
 - a. This Fourth Amendment is the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written

agreements and discussions. This Fourth Amendment may be amended only by an agreement in writing, signed by the parties hereto.

b. This Fourth Amendment is binding upon and shall inure to the benefit of the parties hereto, and their respective successors and assigns.

c. This Fourth Amendment may be executed in 2 or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or any electronic signature process complying with the U.S. federal E-SIGN Act of 2000) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Fourth Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

d. Except as amended and/or modified by this Fourth Amendment, the Lease is hereby ratified and confirmed and all other terms of the Lease shall remain in full force and effect, unaltered and unchanged by this Fourth Amendment. In the event of any conflict between the provisions of this Fourth Amendment and the provisions of the Lease, the provisions of this Fourth Amendment shall prevail. Whether or not specifically amended by this Fourth Amendment, all of the terms and provisions of the Lease are hereby amended to the extent necessary to give effect to the purpose and intent of this Fourth Amendment.

[Signatures are on the next page.]

IN WITNESS WHEREOF, the parties hereto have executed this Fourth Amendment as of the day and year first above written.

LANDLORD:

ARE-MA REGION NO. 64, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

/s/ Jackie Clem
By: Jackie Clem
Senior Vice President, RE Legal Affairs

TENANT:

MODERNATX, INC.,
a Delaware corporation

/s/ Juan Andres
By: Juan Andres
Its: Chief Tecnical Operations and Quality Officer

OMNIBUS AMENDMENT TO THREE MODERNA LEASE AGREEMENTS

THIS OMNIBUS AMENDMENT TO THREE MODERNA LEASE AGREEMENTS (this "Amendment") is made as of December 30, 2021, by and between **ARE-MA REGION NO. 92, LLC**, a Delaware limited liability company and owner of the property commonly known as One Investors Way, Norwood, Massachusetts ("One Investors Landlord"), **ARE-MA REGION NO. 64, LLC**, a Delaware limited liability company and owner of the property commonly known as 100 Tech Drive, Norwood, Massachusetts ("100 Tech Landlord"), and **ARE-MA REGION NO. 83, LLC**, a Delaware limited liability company and owner of the property commonly known as One Upland Road, Norwood, Massachusetts ("One Upland Landlord") (collectively, "Landlords"), and **MODERNATX, INC.**, a Delaware corporation ("Tenant").

RECITALS

A. One Investors Landlord and Tenant are parties to that certain Lease Agreement dated as of April 16, 2021 (the "One Investors Lease"), with respect to the real property and improvements thereon located at 1 Investors Way, Norwood, Massachusetts, as more particularly described in the One Investors Lease.

B. 100 Tech Landlord (as successor-in-interest to Campanelli-TriGate Norwood Upland, LLC) and Tenant are parties to that certain Net Lease dated as of August 29, 2016, as amended by that certain First Amendment to Lease dated as of April 10, 2017, as further amended by that certain Second Amendment to Lease dated as of March 16, 2018, as further amended by that certain Third Amendment to Lease dated as of September 11, 2018, as further amended by that certain Fourth Amendment to Lease dated as of March 28, 2019 (as amended, the "100 Tech Lease"), with respect to the real property and improvements thereon located at 100 Tech Drive, Norwood, Massachusetts, as more particularly described in the 100 Tech Lease.

C. One Upland Landlord (as successor-in-interest to BR Norwood Owner, LLC) and Tenant are parties to that certain Lease Agreement dated as of October 10, 2007, as amended by that certain First Amendment to Lease dated as of February 15, 2019, as further amended by that certain Second Amendment to Lease dated as of February 15, 2019, as further amended by that certain First Amendment to Lease Guaranty dated April 30, 2019, and as further amended by that certain Third Amendment to Lease Agreement dated as of May 21, 2020 (as amended, the "One Upland Lease"). Collectively, the One Investors Landlord, 100 Tech Landlord, and One Upland Landlord shall be referred to herein as the "Landlords", and the One Investors Lease, 100 Tech Lease, and One Upland Lease shall be referred to herein as the "Leases".

D. Landlords and Tenant desire to extend the terms of the Leases and otherwise amend the Leases upon the terms and conditions contained herein. All capitalized terms not defined herein shall have the same meaning ascribed to such terms in the Leases.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual promises and agreements hereinafter set forth, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlords and Tenant hereby agree as follows:

1. Term. The terms of the Leases are extended to and including September 30, 2042.

2. Base Rent. The base rent schedules for each of the Leases is hereby modified as follows:

- a. One Investors Lease: The definition of “Base Rent” set forth on page 1 of the One Investors Lease is hereby deleted in its entirety and replaced with the following:

“Beginning on the Rent Commencement Date, annual Base Rent shall be \$6,466,500.00, subject to annual increases on the Adjustment Date as set forth herein.

<u>Year</u>	<u>Annual Base Rent</u>	<u>Monthly Base Rent</u>	<u>Base Rent/RSF</u>
February 17, 2022 – February 28, 2023	\$6,466,500.00	\$538,875.00	\$26.94
March 1, 2023 – February 29, 2024	\$6,660,495.00	\$555,041.25	\$27.75
March 1, 2024 – February 28, 2025	\$6,860,310.00	\$571,692.50	\$28.58
March 1, 2025 – February 28, 2026	\$7,066,119.00	\$588,843.25	\$29.44
March 1, 2026 – February 28, 2027	\$7,278,103.00	\$606,508.58	\$30.33
March 1, 2027 – February 29, 2028	\$7,496,446.00	\$624,703.83	\$31.24
March 1, 2028 – February 28, 2029	\$7,721,339.00	\$643,444.92	\$32.17
March 1, 2029 – February 28, 2030	\$7,952,979.00	\$662,748.25	\$33.14
March 1, 2030 – February 28, 2031	\$8,191,569.00	\$682,630.75	\$34.13
March 1, 2031 – February 29, 2032	\$8,437,316.00	\$703,109.67	\$35.16
March 1, 2032 – February 28, 2033	\$8,690,435.00	\$724,202.92	\$36.21

March 1, 2033 – February 28, 2034	\$8,951,148.00	\$745,929.00	\$37.30
March 1, 2034 – February 28, 2035	\$9,847,200.00	\$820,600.00	\$41.03
March 1, 2035 – February 29, 2036	\$10,142,400.00	\$845,200.00	\$42.26
March 1, 2036 – February 28, 2037	\$10,447,200.00	\$870,600.00	\$43.53
March 1, 2037 – February 28, 2038	\$10,761,600.00	\$896,800.00	\$44.84
March 1, 2038 – February 28, 2039	\$11,085,600.00	\$923,800.00	\$46.19
March 1, 2039 – February 29, 2040	\$11,419,200.00	\$951,600.00	\$47.58
March 1, 2040 – February 28, 2041	\$11,762,400.00	\$980,200.00	\$49.01
March 1, 2041 – September 30, 2042	\$12,115,272.00	\$1,009,606.00	\$50.48

- b. 100 Tech Lease: Schedule I of the 100 Tech Lease is hereby deleted in its entirety and replaced with the Fixed Rent set forth below.

<u>Lease Year</u>	<u>Annual Fixed Rent</u>	<u>Monthly Fixed Rent</u>
October 1, 2017 – September 30, 2018	\$6,193,317.90	\$516,109.83
October 1, 2018 – September 30, 2019	\$6,348,150.85	\$529,012.57
October 1, 2019 – September 30, 2020	\$6,506,854.62	\$542,237.89
October 1, 2020 – September 30, 2021	\$6,669,525.98	\$555,793.83
October 1, 2021 – September 30, 2022	\$6,836,264.13	\$569,688.68

October 1, 2022 – September 30, 2023	\$7,007,170.74	\$583,930.90
October 1, 2023 – September 30, 2024	\$7,182,350.01	\$598,529.17
October 1, 2024 – September 30, 2025	\$7,361,908.76	\$613,492.40
October 1, 2025 – September 30, 2026	\$7,545,956.48	\$628,829.71
October 1, 2026 – September 30, 2027	\$7,734,605.39	\$644,550.45
October 1, 2027 – September 30, 2028	\$7,927,970.53	\$660,664.21
October 1, 2028 – September 30, 2029	\$8,126,169.79	\$677,180.82
October 1, 2029 – September 30, 2030	\$8,329,324.03	\$694,110.34
October 1, 2030 – September 30, 2031	\$8,537,557.13	\$711,463.09
October 1, 2031 – September 30, 2032	\$8,750,996.06	\$729,249.67
October 1, 2032 – September 30, 2033	\$9,626,095.68	\$802,174.64
October 1, 2033 – September 30, 2034	\$9,914,878.56	\$826,239.88
October 1, 2034 – September 30, 2035	\$10,212,324.96	\$851,027.08
October 1, 2035 – September 30, 2036	\$10,518,694.68	\$876,557.89
October 1, 2036 – September 30, 2037	\$10,834,255.56	\$902,854.63
October 1, 2037 – September 30, 2038	\$11,159,283.24	\$929,940.27
October 1, 2038 – September 30, 2039	\$11,494,061.76	\$957,838.48
October 1, 2039 – September 30, 2040	\$11,838,883.56	\$986,573.63

October 1, 2040 – September 30, 2041	\$12,194,050.08	\$1,016,170.84
October 1, 2041 – September 30, 2042	\$12,559,871.64	\$1,046,655.97

- c. One Upland Lease: Article I of the One Upland Lease is hereby amended by modifying the following subsections as follows:

1.04 Term and Possession: The Initial Term of the Lease is hereby extended for a period expiring on September 30, 2042 (the “Expiration Date”). The Lease is hereby amended so that all references to the “Lease Term” and the “Initial Term” in the Lease shall refer to the Initial Term as extended hereunder, and the new Expiration Date as modified herein.

(a) From August 1, 2020, Base Rent for the Premises shall be paid as follows and all references to the “Base Rent” in the Lease shall be deemed to refer to the Base Rent set forth in the table below:

<u>Period</u>	<u>Annual Base Rent</u>	<u>Monthly Base Rent</u>
8/1/2020-7/31/2021	\$5,700,024.47	\$475,002.04
8/1/2021-7/31/2022	\$5,794,593.41	\$482,882.78
8/1/2022-7/31/2023	\$5,794,593.41	\$482,882.78
8/1/2023-7/31/2024	\$5,891,999.42	\$490,999.95
8/1/2024-7/31/2025	\$5,891,999.42	\$490,999.95
8/1/2025-7/31/2026	\$5,992,327.61	\$499,360.63
8/1/2026-7/31/2027	\$5,992,327.61	\$499,360.63
8/1/2027-7/31/2028	\$6,095,665.65	\$507,972.14
8/1/2028-7/31/2029	\$6,095,665.65	\$507,972.14
8/1/2029-7/31/2030	\$6,202,103.82	\$516,841.99
8/1/2030-7/31/2031	\$6,202,103.82	\$516,841.99
8/1/2031-7/31/2032	\$6,311,735.15	\$525,977.93
8/1/2032-7/31/2033	\$6,311,735.15	\$525,977.93
8/1/2033-7/31/2034	\$6,424,655.41	\$535,387.95
8/1/2034-7/31/2035	\$6,424,655.41	\$535,387.95
8/1/2035-9/30/2035	2 month period	\$545,080.27
10/1/2035-9/30/2036	\$7,195,227.20	\$599,602.27
10/1/2036-9/30/2037	\$7,411,084.02	\$617,590.34
10/1/2037-9/30/2038	\$7,633,416.54	\$636,118.05
10/1/2038-9/30/2039	\$7,862,419.04	\$655,201.59
10/1/2039-9/30/2040	\$8,098,291.61	\$674,857.63
10/1/2040-9/30/2041	\$8,341,240.36	\$695,103.36
10/1/2041-9/30/2042	\$8,591,477.57	\$715,956.46

3. Extension Rights. In lieu of any existing extension rights in the Leases, Tenant is hereby granted three (3) consecutive extension rights for each of the three Leases. Accordingly, the Leases are hereby amended as follows:

- a. One Investors Lease: Section 41(a) of the One Investors Lease is hereby amended by deleting “two (2) consecutive rights” and replacing it with “three (3) consecutive rights”.
- b. 100 Tech Lease: Section 10.2 of the 100 Tech Lease is hereby amended by deleting the first sentence in its entirety and replacing it with the following:

“Tenant shall have three (3) consecutive rights to extend the term of this Lease for five (5) years each (each, an “Extension Term”), provided that Tenant shall give Landlord notice of Tenant's exercise of such option no sooner than twenty-four

(24) months and no later than eighteen (18) months prior to the expiration of the then current Term, and provided further that Tenant shall not be in default at the time of giving such notice under this Lease beyond applicable notice and cure periods.”

- c. One Upland Lease: Section 1.04 of the One Upland Lease is hereby amended by deleting “four options to extend” and replacing it with “three options to extend”.

4. Alterations and Restoration. For ease of administration and consistency, Landlords and Tenant agree that the process for approval by Landlords of Tenant’s proposed Tenant Improvements (as defined below), and the restoration obligations associated therewith, shall be governed by the One Investors Lease, notwithstanding any contrary provisions of the 100 Tech Lease or One Upland Road Lease. The Landlords acknowledge and agree that the Tenant Improvements will be designed and performed in furtherance of a master planning effort undertaken by Tenant and reviewed by the Landlords, the effect of which will be to treat the three Premises as a unified whole, without regard to property line and Premises boundaries. Each Landlord agrees to be reasonable in reviewing and approving applicable Tenant Improvements on its Premises, regardless of the location of such Tenant Improvements within the overall project. Notwithstanding anything to the contrary contained in the One Investors Lease regarding restoration of Installations (as defined in the One Investors Lease), Tenant shall have no obligation to remove and restore at the end of the Term any new buildings or expansions of existing buildings, landscaping, planted areas, walks, roadways, parking, and other new installations and improvements on the Premises outside of the existing buildings.

5. Tenant Improvement Allowance. Each of the three Landlords agrees to provide an additional tenant improvement allowance of \$60.00 per rentable square foot of the applicable Premises, for an aggregate total of \$41,010,780.00 (the “2021 Tenant Improvement Allowance” or “2021 TIA”), broken down as follows: \$14,400,000.00 under the One Investors Lease, \$12,025,860.00 under the 100 Tech Lease, and \$14,584,920.00 under the One Upland Lease. Notwithstanding that the 2021 TIA has been allocated to each of the separate Landlords, Tenant is not bound by such allocation, and the Landlords acknowledge and agree that Tenant may apply any amount of the 2021 TIA to Tenant Improvements across the three Premises as Tenant sees fit, without regard to each Landlord’s portion of the total. Notwithstanding contrary provisions of the Leases governing disbursement of tenant allowance funds, the 2021 Tenant Improvement Allowance shall be disbursed and used as follows:

- a. Tenant shall have no right to any portion of the 2021 TIA that is not disbursed before the second anniversary of the date hereof.
- b. Costs. The 2021 TIA shall be used solely for the payment of design (including A&E drawings), permits and construction, and construction management costs in connection with the construction of tenant improvements, site work, new structures and other hard construction costs (the “Tenant Improvements”) at the properties covered by the three Leases (collectively, the “TI Costs”). The 2021 TIA shall not be used to purchase any furniture, personal property or other non-building system materials or equipment, including, but not be limited to, non-ducted biological safety cabinets and other scientific equipment not incorporated into the Tenant Improvements; provided,

however, the 2021 TIA may be used for Tenant's voice and data cabling, special electrical power distribution, telephone and security systems.

Landlord shall have no obligation to bear any portion of the cost of any of the Tenant Improvements except to the extent of the 2021 TIA and except to the extent that any remaining contributions or allowances remain under each of the existing Leases as of the date hereof.

- c. Procedure. During the course of construction of the Tenant Improvements, Landlord shall reimburse Tenant for TI Costs once a month (such reimbursement not to exceed, in the aggregate, the amount of the 2021 TIA) against a draw request in Landlord's standard form, containing evidence of payment of such TI Costs by Tenant and such certifications, lien waivers (including a conditional lien release for each progress payment and unconditional lien releases for the prior month's progress payments), inspection reports and other matters as Landlord customarily obtains, to the extent of Landlord's approval thereof for payment, no later than the last day of the calendar month immediately following the calendar month in which the draw request was made. Upon completion of the Tenant Improvements (and prior to any final disbursement of the 2021 TIA), Tenant shall deliver to Landlord: (i) sworn statements setting forth the names of all contractors and first tier subcontractors who did the work and final, unconditional lien waivers from all such contractors and first tier subcontractors; (ii) as-built plans (one copy in print format and two copies in electronic CAD format) for such Tenant Improvements; (iii) a certification of substantial completion in Form AIA G704, (iv) a certificate of occupancy for the premises covered by each Lease, to the extent not already delivered; and (v) copies of all operation and maintenance manuals and warranties affecting the premises covered by each Lease.
- d. Nonpayment; Offset Right; Disputes. If any Landlord fails timely to pay any portion of the 2021 TIA when such portion is properly due to Tenant and as to which Tenant has satisfied each of the foregoing requisition conditions, and such failure shall continue for 30 days after written notice from Tenant to such Landlord (which such notice shall describe in detail the basis on which Tenant asserts that such Landlord has wrongfully failed to disburse such amount), then Tenant, provided no Default has occurred and is continuing, may deliver a second notice to such Landlord that includes in at least 14 point-type and all capitals (with the rest of the notice in standard font and type-size) the phrase "FAILURE TO IMMEDIATELY RESPOND COULD RESULT IN THE FORFEITURE OF RIGHTS" (an "Offset Notice"), which notice shall specify the portion of the TI Allowance that has not been timely paid and the date upon which request for payment was first sent to such Landlord, and, if such Landlord fails to disburse the amount expressly referenced in the Offset Notice within 10 business days, then Tenant shall have the right to have such unpaid amount credited against the next installment(s) of Base Rent thereafter due under the applicable Lease, until such sums due Tenant have been fully paid by such Landlord or fully credited and accounted for; provided however, that the amount so offset by Tenant in any calendar month shall not exceed 20% of the amount of the monthly installment of Base Rent payable by Tenant to Landlord under the applicable Lease with respect to such calendar month. If, however, Landlord notifies Tenant prior to the expiration of such 10 business day period that Landlord disputes that Landlord has wrongfully

failed to disburse the amount claimed by Tenant, and if Landlord and Tenant are not able to reach agreement with respect to such dispute (with Landlord disbursing any undisputed amounts which Landlord is required to disburse under this Work Letter) within 10 business days after Tenant's receipt of a such notice from Landlord, then the parties shall submit such dispute to arbitration conducted by the American Arbitration Association in Boston, Massachusetts in accordance with the "Expedited Procedures" of its Commercial Arbitration Rules, in which case Base Rent shall not be offset by such disputed amount unless and until Tenant prevails in such arbitration and the arbitrator concludes that Tenant has the right to such offset right and determines the amount owed to Tenant by Landlord, if any, that is to be offset against Base Rent. All costs associated with arbitration shall be awarded to the prevailing party as determined by the arbitrator.

- e. Tenant Improvement Progress Reports. On or before the 10th day of each calendar month during the course of design and construction of the Tenant Improvements, Tenant shall deliver to Landlords a Tenant Improvement progress report in a form provided by Landlords completed to provide all of the most up-to-date information regarding Tenant's progress with respect the design and construction of the Tenant Improvements.

6. Cross-Default. Tenant agrees that a "Default" under the One Investors Lease or "Event of Default" under the 100 Tech Lease and One Upland Lease shall automatically constitute a Default or Event of Default, as applicable, under all three Leases.

7. Authority. Landlords represent and warrant to Tenant that they have the right, power and authority to execute and deliver this Amendment and to perform their obligations hereunder, and this Amendment is a valid and binding obligation of Landlords enforceable against Landlords in accordance with the terms hereof. Tenant represents and warrants to Landlords that it has the right, power and authority to execute and deliver this Amendment and to perform its obligations hereunder, and this Amendment is a valid and binding obligation of Tenant enforceable against Tenant in accordance with the terms hereof. Tenant acknowledges and agrees that Landlords are in full compliance with the terms of the Leases and no event exists or has occurred that constitutes or could ripen into a Landlord default under the Leases.

8. Brokerage. Landlords and Tenant each hereby represents that, other than Newmark Grubb Knight Frank and Jones Lang LaSalle (collectively, the "Brokers"), it has not dealt with any broker, agent or other person entitled to a commission, compensation, or fee with respect to the transactions contemplated by this Amendment. Landlords and Tenant each hereby agree to defend, indemnify, and hold harmless the other, and its successors and assigns, against and from all claims, losses, liabilities, and expenses, including, without limitation, reasonable attorneys' fees, arising out of any claim by any broker, agent, or other person or entity, other than the Brokers, claiming a commission or other form of compensation based upon alleged dealings with the indemnifying party with respect to this Amendment. Landlords shall be responsible to pay the commission due to the Brokers pursuant to a separate agreement.

9. Ratification; Conflict; Amendment. Except as amended herein, the Leases shall remain in full force and effect and the parties hereto ratify and reconfirm the Leases. On and after the date hereof, each reference in the Leases to "this Lease," "the Lease," "hereunder," "hereof," or words of like import, and each reference to the Lease in any other agreements, documents, or instruments executed and delivered pursuant to, or in connection with, the Leases, will mean and be a reference to the Leases as amended by this Amendment. In the

event of any conflict between this Amendment and the Leases, the provisions of this Amendment shall control. No amendment or modification of this Amendment, and no further amendment or modification of the Leases, will be effective unless it is in writing and signed by Landlords and Tenant.

10. Governing Law. This Amendment shall be governed by the laws of the Commonwealth of Massachusetts without regard to its conflict of law provisions.

11. Counterparts. This Amendment may be executed in as many counterparts as the parties hereto may deem necessary or convenient, and each such counterpart shall be deemed an original but all of which, together, shall constitute but one and the same document. Counterparts may be delivered via electronic mail (including PDF or any electronic signature process complying with the U.S. federal ESIGN Act of 2000) or other transmission method, and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes. Electronic signatures shall be deemed original signatures for purposes of this Amendment and all matters related thereto, with such electronic signatures having the same legal effect as original signatures.

12. Successors and Assigns. The provisions hereof shall inure to the benefit of, and be binding upon, the parties hereto and their successors and permitted assigns.

13. Attorneys' Fees. In the event of a dispute between the parties, the prevailing party shall be entitled to have its reasonable attorneys' fees and costs paid by the other party.

14. Acknowledgment. Tenant and Landlords each acknowledge that it has read the provisions of this Amendment, understands them, and is bound by them. Time is of the essence in this Amendment.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the parties hereto have duly executed and delivered this Amendment under seal as of the day and year first above written.

LANDLORDS:

ARE-MA REGION NO. 92, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

/s/ Mark Hikin
By: Mark Hikin
Its: Vice President, RE Legal Affairs

ARE-MA REGION NO. 64, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

/s/ Mark Hikin
By: Mark Hikin
Its: Vice President, RE Legal Affairs

ARE-MA REGION NO. 83, LLC,
a Delaware limited liability company

By: ALEXANDRIA REAL ESTATE EQUITIES, L.P.,
a Delaware limited partnership,
managing member

By: ARE-QRS CORP.,
a Maryland corporation,
general partner

/s/ Mark Hikin
By: Mark Hikin
Its: Vice President, RE Legal Affairs

TENANT:

MODERNATX, INC.,
a Delaware corporation

/s/ David Meline
By: David Meline
Its: Chief Financial Officer



December 28, 2020

Corinne Le Goff, Pharm. D., MBA

Re: Offer of Employment by ModernaTX, Inc.

Dear Corinne,

ModernaTX, Inc. (together with its affiliates, the "Company") is pleased to confirm, contingent on receiving appropriate references and the successful completion of a background check/drug screen, its offer to employ you as Chief Commercial Officer, reporting to the Chief Executive Officer. Your effective date of hire will be on or before January 19, 2021 (the "Start Date"), and you will perform services for the Company as a regular, full-time employee. The initial terms of your employment, should you accept this offer, are set forth below.

This is a full-time, exempt level position. Your base salary will be at the rate of \$625,000.00 (USD) per year. All wages will be paid in accordance with the Company's normal biweekly pay schedule for salaried employees, and is subject to change by the Company. Your base salary will be subject to periodic review and adjustment at the Company's discretion.

In addition to the foregoing, upon your commencement of employment with the Company, you will be paid a one-time signing bonus of \$300,000.00 less applicable taxes (the "Signing Bonus"). You acknowledge and agree that you will repay the Signing Bonus to the Company within 10 days of your last day of employment if you voluntarily terminate your employment with the Company or your employment is terminated for cause (as determined by the Company) during the first 24 months of your employment. That amount may be collected by the Company, either directly or indirectly, from any (i) payment of any kind due to you from the Company or any affiliate thereof including, without limitation, accrued wages, vacation, final wages, and expense reimbursements to the fullest extent permitted by applicable law; and/or (ii) the forfeiture or cancellation of any equity interest owned by you in the Company or any subsidiary or affiliate thereof, whether now existing or hereafter formed, and regardless of the form such equity interest (e.g., common units, incentive units (also referred to as profits interests), options to acquire common units or otherwise).

You will be eligible to earn an annual performance bonus. The Company will initially target the bonus at up to 75% of your annual salary rate (pro-rated based on your Start Date, provided that your Start Date is on or before the first Monday of October of the applicable calendar year). If your Start Date is after the first Monday of October, you will not be eligible for a bonus for the calendar year in which you were hired. The actual bonus percentage is discretionary and will be subject to the Company's assessment of your performance, as well as business conditions at the Company. The bonus also will be subject to approval by and adjustment at the discretion of the Company and the terms of any applicable bonus plan. The bonus, if any, will be paid no later than March 15 of the calendar year following the calendar year to which such bonus relates. You must be employed on the date a bonus is paid to receive that bonus.

Subject to the commencement of your employment with the Company, the Company will recommend to the Board of Directors (the "Board") of the Company's parent entity ("Parent"), that you be eligible to participate in Moderna's equity incentive program and be granted, at such time as the Board so determines, an equity award equivalent to a total value of \$8,000,000.00 as of the grant date (such equity award is referred to as the "New Hire Equity Award"). Subject to the Board's approval of the New Hire

Equity Award, the New Hire Equity Award will vest according to the following schedule: 25% of the New Hire Equity Award will vest on the first anniversary of the date of grant, and the remaining 75% of the New Hire Equity Award will vest in equal calendar quarterly installments over the next three (3) years, provided that, in each case, you continue to provide continuous services to the Company as of each such vesting date. The New Hire Equity Award is subject to our "Your Equity Selection" (YES) program. You may choose to have your award delivered to you in one of the following mixes of Non-Qualified Stock Options and/or Restricted Stock Units:

- 100% of the value delivered in the form of Non-Qualified Stock Options.
- 75% of the value delivered in the form of Non-Qualified Stock Options and 25% in value delivered in the form of Restricted Stock Units. This is the default choice if no selection is made.
- 50% of the value delivered in the form of Non-Qualified Stock Options and 50% in value delivered in the form of Restricted Stock Units.

You will receive an email from the Compensation Team at the Company to register your selection prior to your grant date. In the event of a stock split, stock consolidation or similar event prior to the grant of the New Hire Equity Award, the number of shares subject thereto shall be adjusted proportionately. The grant price of the New Hire Equity Award will be equal to the closing price on the day of grant. The grant of the New Hire Equity Award will be conditioned upon, among other things, your execution of all necessary documentation relating to the New Hire Equity Award as determined by the Company (all such documentation is collectively referred to as the "New Hire Equity Award Documentation"). The New Hire Equity Award will be subject to the terms and conditions set forth in the New Hire Equity Award Documentation.

Further, subject to the Board's approval, and provided your start date is on or before the first Monday of October of the applicable calendar year, you will be eligible to receive an annual equity award related to your performance for the eligible performance period (the "Annual Equity Award"). Annual Equity Awards typically will be issued in the first quarter of the year following the performance period. Your annual grants will be based on a combination of market data and performance. You will receive an annual grant that will be a mix of stock options, RSU's, and potentially PSU's subject to the current executive pay policies in place. The current range is between \$2M-\$4M. Your first Annual Equity Award, if any, will be pro-rated based upon your start date. Targets may be modified up or down based on your individual performance. Annual equity guidelines are subject to change and may be updated based on market conditions.

You may be required to relocate to the Greater Boston area, as applicable, by December 31, 2021, or as mutually agreed upon by both parties. The Company will pay reasonable costs associated with your relocation (the "Relocation Expenses") in accordance with the Employee Relocation Guidelines that are in effect at the time of the initiation of your relocation case. The Company will determine in its reasonable judgment what portion, if any, of your Relocation Expenses are for nondeductible expenses in accordance with applicable law and will comply with associated withholding and tax reporting obligations. You acknowledge and agree that you will repay the Relocation Expenses to the Company within 10 days of your last day of employment if you voluntarily terminate your employment with the Company or your employment is terminated for cause (as determined by the Company) within 24 months of the initiation of your relocation case. That amount may be collected by the Company, either directly or indirectly, from any (i) payment of any kind due to you from the Company or any affiliate thereof including, without limitation, accrued wages, vacation, final wages, and expense reimbursements to the fullest extent permitted by applicable law; and/or (ii) the forfeiture or cancellation of any equity interest owned by you in the Company or any subsidiary or affiliate thereof, whether now existing or hereafter formed, and regardless of the form such equity interest (e.g., common units, incentive units (also referred to as profits interests), options to acquire common units or otherwise).

In addition to your compensation, you may take advantage of various benefits offered by the Company from time to time, subject to any eligibility requirements. Currently the Company provides group medical and dental insurance, short term disability coverage, group life insurance and a 401(k)

plan. These benefits, of course, may be modified, changed or eliminated from time to time at the sole discretion of the Company, and the provision of such benefits to you in no way changes or impacts your status as an at-will employee. Where a particular benefit is subject to a formal plan (for example, medical insurance or life insurance), eligibility to participate in and receive any particular benefit is governed solely by the applicable plan document. Should you ever have any questions about Company benefits, you should ask for a copy of the applicable plan document. You will also be eligible for vacation pursuant to the Company's policies in effect from time to time.

All forms of compensation referred to in this offer letter are subject to reduction to reflect applicable withholding and payroll taxes and other deductions required by law.

You acknowledge and agree that employment with the Company is "at will." You are not being offered employment for a definite period of time, and either you or the Company may terminate the employment relationship at any time and for any reason without prior notice and without additional compensation to you. Similarly, this offer letter sets forth the initial terms and conditions of your employment, which are subject to change at any time at the Company's discretion. Although your job duties, title, reporting structure, compensation and benefits, as well as the Company's personnel policies and procedures, may change from time to time, the "at-will" nature of your employment may only be changed by a written agreement signed by you and the Chief Executive Officer, which expressly states the intention to modify the at-will nature of your employment.

You are being hired as a Massachusetts employee and you must live and work in Massachusetts as a material condition of your employment. However, due to factors that affect your ability to relocate immediately, including the COVID-19 pandemic, you will be permitted to commence employment by working remotely from your home in California until your full relocation to Cambridge, Massachusetts by August 1, 2021. You will be taxed in your home state until you relocate. It is understood that the Company may change your normal place of work according to the Company's future needs.

As a condition of the commencement of your employment, you are required to enter into an Employee Confidentiality, Assignment, Nonsolicitation and Noncompetition Agreement (the "Restrictive Covenants Agreement", a copy of which is enclosed with this offer letter. This offer is conditioned on your representation that you are not subject to any confidentiality, non-competition agreement or any other similar type of restriction that may affect your ability to devote full time and attention to your work at the Company. If you have entered into any agreement that may restrict your activities on behalf of the Company, please provide me with a copy of the agreement as soon as possible. You further represent that you have not used and will not use or disclose any trade secret or other proprietary right of any previous employer or any other party.

The Immigration Reform and Control Act requires employers to verify the employment eligibility and identity of new employees. You will receive a Form I-9 that you will be required to complete. Please bring the appropriate documents listed on that form with you when you report for work. We will not be able to employ you if you fail to comply with this requirement.

This offer letter and the enclosed Restrictive Covenants Agreement constitute the complete agreement between you and the Company, contain all of the terms of your employment with the Company and supersede any prior agreements, representations or understandings (whether written, oral or implied) between you and the Company.

Please indicate your acceptance of this offer by signing and dating this offer letter and the enclosed Restrictive Covenants Agreement (PDF by email) and returning it by January 1, 2021.

Corinne, we look forward to your joining the Company and are pleased that you will be working with us to build a transformative company for patients.

Very truly yours,

ModernaTX, Inc.

By: April Eldred

Title: Vice President, Talent Acquisition

/s/ April Eldred

Accepted and Agreed:

Corinne Le Goff, Pharm. D, MBA

/s/ Corinne Le Goff

12/29/2020

Date



200 Technology Square • Cambridge, MA 02139
phone 617-714-6500 • fax 617-583-1998

Personal and Confidential

November 11, 2021

Corinne Le Goff

[***]

[***]

Re: Executive Separation and Transitional Services Agreement

Dear Corinne:

In accordance with the Amended and Restated Executive Severance Plan (the "Severance Plan") of Moderna Inc. (individually, and together with any direct and indirect parents, subsidiaries, and affiliates, the "Company"), this executive separation and transitional services agreement (the "Agreement") sets forth the terms of your continued employment with the Company through the earliest of (i) the close of business on December 17, 2021 (the "Anticipated Separation Date") or (ii) such earlier date when your employment is terminated (a) by the Company with Cause, (b) due to your death or Disability, or (c) by you (such actual last day of employment, the "Separation Date")¹. For purposes of this Agreement, the time period between the date first set forth above and the Separation Date shall be referred to as the "Transition Period." During the Transition Period you will continue to receive your salary and benefits (subject to eligibility under any applicable benefits plans) and continue to vest in your outstanding equity, but you will not be expected to come into the office or work remotely unless otherwise directed by the Company's Chief Executive Officer ("CEO"). For the avoidance of doubt, as of the date of this Agreement, the Company characterizes your termination as a termination without Cause. In the event that the Company should seek to terminate your employment for Cause following the date of this Agreement, it will promptly notify you in writing. Any such termination for Cause shall become effective within three (3) business days of delivery of the notice, unless the circumstances giving rise to the for Cause termination are cured within such three (3) business days.

Regardless of whether you enter into the Agreement, the following bulleted terms and obligations (the "Accrued Benefits") shall apply:

- You will continue to participate in the Company's Severance Plan and will be entitled to any benefits and payments thereunder in the event of a Qualified Termination Event (as defined in the Severance Plan), subject to the terms and conditions of the Severance Plan.
- On the Separation Date, the Company shall pay you for all salary plus any accrued but unused vacation to which you are entitled through the Separation Date.

¹ "Cause" is defined by the Company's Amended and Restated Executive Severance Plan effective as of November 4, 2018 (the "Severance Plan"). "Disability" is defined as your inability to perform the essential functions of your employment with the Company, with or without a reasonable accommodation, for more than 120 consecutive days, unless a longer period is required by federal or applicable state law, in which case that longer period would apply.

- Your eligibility to participate in the Company's health, dental and vision plans will cease on the last day of the month in which the Separation Date occurs. You may elect to continue your health, dental and vision benefits in accordance with and subject to the law known as COBRA. You will be notified by separate memoranda of your rights under COBRA including payment obligations. You will participate under COBRA in accordance with the provisions of Section 3(e) below.
- Your eligibility to participate in the Company's other employee benefit plans and programs will cease on the Separation Date in accordance with the terms and conditions of each of those benefit plans and programs. Your rights to benefits, if any, are governed by the terms and conditions of those benefit plans and programs. If you are currently participating in the Company's 401(k) plan, deductions for the 401(k) Plan will end with your December 17, 2021 paycheck, *provided* this date is the Separation Date. You will receive information by mail concerning 401(k) plan rollover procedures should you be a participant in this program. Without limiting the generality of the foregoing and for the avoidance of doubt, you are not eligible to receive any bonus or other forms of incentive compensation with respect to you working for the Company during fiscal year 2021 or thereafter, except as set forth in Section 3(b) below and *provided* you meet the conditions set forth in Section 2.
- If applicable, you shall also have the right to retain any and all vested restricted stock units and to exercise any and all vested options that you hold to purchase equity of the Company, and any such exercise shall be made in accordance with, and shall be subject to, the terms of any and all applicable unit option and grant plans, equity incentive plans and all other equity award plans and all agreements relating to any of the foregoing (all of the foregoing are collectively referred to as the "Equity Documents"), including without limitation the time limits on exercise. Pursuant to the terms of the Equity Documents, all unvested restricted stock units and stock options you may hold will expire and be null and void as of the Separation Date. If you have any questions about your equity interests, please contact the Company's Chief Legal Officer.
- You are obligated, to the maximum extent permitted by applicable law, to comply with each of the obligations set forth in your Employee Confidentiality, Assignment, Noncompetition and Nonsolicitation Agreement dated as of December 29, 2020 (the "Restrictive Covenants Agreement"), a copy of which is being provided to you with this Agreement as Exhibit A.

Except as noted above, the payments and other terms set forth above will not be affected by whether or not you agree to the terms set forth below.

In addition to the above-described non-contingent terms, you will be entitled to the Severance Benefits (described in Section 3 below) if you meet the Conditions (as defined in Section 2 below). If you enter into this Agreement, you acknowledge that you are doing so voluntarily.

With those understandings, you and the Company agree as follows:

1. Matters Relating to the Transition Period. If you enter into, do not revoke, and comply with this Agreement (including, without limitation the Conditions set forth in Section 2 below), your employment with the Company will end on the Anticipated Separation Date, unless your employment is terminated on an earlier date in accordance with this Agreement (a) by the Company, with or without Cause, (b) due to your death or Disability, or (c) by you. During the Transition Period, you will not report to the Company's offices or perform any duties for or on behalf of the Company unless specifically requested by the Company's CEO. Notwithstanding the foregoing, you will make yourself available to answer any questions from the CEO or any other Company executive related to the Company or to transitioning

matters to other employees. Any change to your duties as set forth herein shall not (a) constitute Good Reason as defined in and for purposes of the Severance Plan, and you hereby waive the application of Good Reason to your employment from the date of this Agreement to the Separation Date, or (b) alter any of your obligations under the Restrictive Covenants Agreement. On the earliest of (i) the Separation Date or (ii) a request by the Company, you will be deemed to have resigned from all officer positions that you hold with the Company or any of its respective subsidiaries and affiliates. You shall execute any documents in reasonable form as may be requested by the Company to confirm or effectuate any such resignations. With respect to compensation, you will continue to receive your current annual base salary and you will be eligible for employee benefits throughout the Transition Period (subject to your continued eligibility under the Company's benefits plans); *provided, however*, you will not be entitled to any other compensation, incentive compensation, or bonuses during the Transition Period or with respect to any period prior to the Transition Period, except as set forth in Section 3 below and *provided* you meet the conditions set forth in Section 2. In addition, you will continue to vest in your restricted stock units and stock options pursuant to the Equity Documents during the Transition Period. You may exercise any vested options consistent with the terms of the Equity Documents. All unvested restricted stock units and stock options will expire on the Separation Date and be of no further effect, *except* as otherwise set forth in Section 3(c) below and provided you meet the conditions set forth in Section 2.

2. Conditions. Subject to the terms of this Agreement, you will be entitled to continue to be employed at the Company during the Transition Period and receive the Severance Benefits (as defined below) *provided* you satisfy each of the following (collectively, the "Conditions"): (i) you enter into this Agreement during the Consideration Period (defined in Section 22 below), do not revoke it, and comply with it; (ii) your employment is not terminated by the Company for Cause, due to death or Disability or as a result of your voluntary resignation prior to the Anticipated Separation Date; (iii) you work cooperatively and in good faith with the Company during the Transition Period and perform the duties described in Section 1 above to the Company's satisfaction; and (iv) you comply with the Restrictive Covenants Agreement. For the avoidance of doubt, if you resign your employment or the Company terminates your employment for Cause before the Anticipated Separation Date, you will be paid only through the Separation Date, even if that date occurs prior to the Anticipated Separation Date, and you shall not be entitled to any payments from the Company from and after the Separation Date.

3. Severance Benefits. If you satisfy each of the Conditions, the Company will provide you with the following post-employment benefits (collectively, the "Severance Benefits"):

(a) Separation Pay. In accordance with the Severance Plan, the Company shall pay you \$625,000, which amount equals twelve (12) months of your current annual base salary, less applicable deductions and withholdings (the "Separation Pay"). The Company shall pay you the Separation Pay in biweekly payments, beginning on the first regular payroll date following the later of the Separation Date and the Agreement Effective Date (as defined in Section 22).

(b) Bonus Payment. In accordance with the Severance Plan, you will receive a prorated portion, based on your Anticipated Separation Date, of your 2021 annual bonus at 100% of the target amount, which the parties agree to be a total of \$450,721.15 before applicable deductions and withholdings (the "Bonus Payment"). The Company shall pay you the Bonus Payment in biweekly payments, beginning on the first regular payroll date following the later of the Separation Date and the Agreement Effective Date (as defined in Section 22).

(c) Post-Employment Consulting Period. Provided that you satisfy the Conditions, then upon the Separation Date, and with no break in your service relationship for purposes of vesting in your

unvested stock options and restricted stock units, the consulting agreement attached hereto as Exhibit B (the “Consulting Agreement”) will become effective and shall, together with this Agreement, govern the post-employment relationship between you and the Company, pursuant to which you will provide consulting services to the Company related to Commercial operational and strategic matters on an as-needed basis through February 3, 2022 (the “Consulting Period”). For the avoidance of doubt, if this Agreement does not become effective, or if you fail to comply with the Agreement or satisfy all of the Conditions, the Consulting Agreement will be deemed void ab initio and be of no force or effect. As described in greater detail in the Consulting Agreement, during the Consulting Period, you will no longer be an employee of the Company, but instead will be retained as a consultant. For the avoidance of doubt, if the Consulting Agreement does not become effective, then your unvested stock options and restricted stock units will cease vesting on the Separation Date. You will not receive any new equity awards during the Consulting Period.

(d) COBRA Premium Assistance. Regardless of whether you enter into the Agreement, if you elect and remain eligible for COBRA, you may continue to participate in the medical, dental and/or vision care plans which you currently participate in by electing COBRA continuation coverage. If you remain covered under COBRA through at least twelve (12) months following the Separation Date, and in accordance with the Severance Plan, the Company will pay through that date the same portion of the COBRA premium that the Company would pay as its share of the cost of coverage if you were an active employee. However, you will not be entitled to this employer subsidy if, prior to the twelve (12) month anniversary of the Separation date, you become eligible to be covered under other group health care coverage, through a new employer or otherwise. During this Company subsidy period, you will be required to continue paying the employee share of premium payments to secure continued coverage. Thereafter, medical insurance coverage shall be continued only to the extent required by COBRA and only to the extent you timely pay the full premium payments yourself.

(e) Non-Competition and Non-Solicitation.

- i. The non-competition obligation as set forth in Section 9(c) of the Restrictive Covenants Agreement is hereby modified as follows:

1)The defined term “Nucleic Acid-Based Technology” is replaced with the defined term “mRNA-Based Technology”, which shall mean “*technology regarding the research, development, manufacture, use or commercialization of mRNA-based constructs for therapeutic, prophylactic, or diagnostic purposes, including sequence and chemical moieties, sequence engineering, biology, manufacturing, and characterization of any mRNA-based constructs or component thereof.*”

2)The defined term “Delivery Technology” is amended and restated as follows: “*Delivery Technology shall mean technology regarding the research, development, manufacture, use or commercialization of delivery vehicles for mRNA-based cargo.*”

- ii. The non-solicitation obligation set forth in Section 9(a) of the Restrictive Covenants Agreement is hereby amended and restated in its entirety, as follows:

“I shall not, directly or indirectly, in any manner, contact, solicit or transact any business with any of the customers of the Company or with any of its vendors in any way that interferes with the Company’s relationship with such customers or vendors. For

purposes of this Agreement, (i) customers shall include then current customers to which the Company provided products or services during the twelve (12) months prior to the Last Day of Employment (the “One Year Lookback”) that I had significant contact with or learned confidential information about in the course of employment and customer prospects that the Company solicited during the One Year Lookback and that I had significant contact with or learned confidential information about in the course of employment, and (ii) vendors shall include then current vendors and vendors that provided services to or in connection with the Company during the One Year Lookback that I had significant contact with or learned confidential information about in the course of employment.

Except with respect to the amendments as set forth above in this Section 3(e), the terms and conditions of the Restrictive Covenants Agreement remain unchanged and in effect. You acknowledge and reaffirm your post-employment restrictive covenants in the Restrictive Covenants Agreement and that, in exchange for the Severance Benefits (including the narrowing of the non-competition and non-solicitation obligations as set forth in this Section 3(e)), you shall not, directly or indirectly, whether as principal, owner, partner, shareholder, member, director, manager, officer, consultant, agent, employee, co-venturer or otherwise, anywhere in the world, (i) provide any of the types of services that you provided to the Company since December 28, 2020 in connection with any Competitive Business (as defined in the Restrictive Covenants Agreement) or (ii) engage or otherwise participate in any Competitive Business. You expressly agree that your receipt of the Severance Benefits constitutes adequate consideration for the foregoing restrictions and you further acknowledge and agree that if you violate any of the provisions of this section (including but not limited to the covenants set forth in your Restrictive Covenants Agreement, which are expressly reaffirmed and incorporated by reference), the running of the restricted periods will be extended by the time during which you engage in such violation(s), and the Company will not be obligated to provide any further Separation Benefits to you.

4. Early Separation. If your employment ends prior to the Anticipated Separation Date in accordance with this Agreement, the following terms shall apply: if the Company terminates your employment for Cause, you resign or your employment ends due to death or Disability, you will receive the Accrued Benefits, cease vesting in your stock options and restricted stock units as of the Separation Date and will not be eligible for any severance pay or benefits, other than as is stated in this Agreement. For purposes of clarity, termination for Cause, resignation, death or Disability are the only reasons your employment can end before the Anticipated Separation Date.

5. General Release of Claims. In consideration for, among other terms, the opportunity to remain employed through the Transition Period and the Severance Benefits, to which you acknowledge and agree that you would otherwise not be entitled, you voluntarily release and forever discharge the Company, its affiliated and related entities (including, without limitation, direct and indirect parent companies (including, without limitation, Moderna, Inc.), and direct and indirect subsidiaries and direct and indirect affiliates), its and their respective predecessors, successors and assigns, its and their respective employee benefit plans and fiduciaries of such plans, and the past, present and future officers, directors, stockholders, members, managers, employees, attorneys, accountants, agents and representatives of each of the foregoing in their official and personal capacities (collectively referred to as the “Releasees”) generally from all claims, demands, debts, damages and liabilities of every name and nature, known or unknown (“Claims”) that, as of the date when you sign this Agreement, you have, ever had, now claim to have or ever claimed to have had against any or all of the Releasees, to the maximum extent permitted by applicable law. This release includes, without limitation, all Claims: relating to your employment by and termination of employment with the Company; of wrongful discharge; of breach of

contract; of discrimination or retaliation under federal, state or local law (including, without limitation, Claims of discrimination or retaliation under the Americans with Disabilities Act, the Age Discrimination in Employment Act, Title VII of the Civil Rights Act of 1964 or Massachusetts General Laws ch. 151B); under the California Fair Employment and Housing Act (FEHA), the California Labor Code, the California Constitution, and the California Family Rights Act (CFRA); under any other federal or state statute; of defamation or other torts; of violation of public policy; for wages, bonuses, incentive compensation, including without limitation Claims pursuant to the Massachusetts Wage Act, the Massachusetts Overtime Law, and the Massachusetts Payment of Wages Law, vacation pay or any other compensation or benefits; for stock, stock options, unit options, units, profit interests, incentive units, restricted stock units or any other equity interests or rights to acquire equity interests in the Company or any other Releasee; and for damages or other remedies of any sort, including, without limitation, compensatory damages, punitive damages, injunctive relief and attorney's fees. You further represent that you have not filed any Claim against the Releasees in any forum, and you agree not to accept damages of any nature, other equitable or legal remedies for your own benefit or attorney's fees or costs from any of the Releasees with respect to any Claim released by this Agreement. Notwithstanding the foregoing, this general release does not release any Claim: (a) that arises after the Agreement Revocation period has expired, including any rights that may arise under the Equity Documents; (b) for unemployment or workers' compensation benefits; (c) for vested rights under ERISA-covered employee benefit plans as applicable on the date you sign this Agreement; (d) to be covered under the Officer Indemnification Agreement between the Executive and the Company dated December 29, 2020 (the "Indemnification Agreement") and under applicable directors and officers liability insurance for acts or omissions while serving as an officer of the Company; (e) under this Agreement or the Consulting Agreement or (f) that by law cannot be waived. You agree not to accept damages of any nature, other equitable or legal remedies for your own benefit or attorney's fees or costs from any of the Releasees with respect to any Claim released by this Agreement. As a material inducement to the Company to enter into the Agreement, you represent that you have not assigned any Claim to any third party, and that you have not filed any complaints, charges, applications, lawsuits, or arbitrations against the Company or any of the Releasees. To the extent that you have knowledge concerning a potential violation of any federal, state or local law, you represent that you have fully disclosed such information to the Company.

6. Continuing Obligations; Cooperation. You understand and agree that you have been employed in a position of confidence and trust and have had access to information concerning the Company that the Company treats as confidential and the disclosure of which could negatively affect the Company's interests (collectively, the "Confidential Information"). You further agree that you will continue to be bound and will abide by the Restrictive Covenants Agreement, which is hereby incorporated by reference. You hereby agree that to the maximum extent permitted by applicable law, you have not and shall not in any way voluntarily assist, aid or participate in the pursuit of any claims or actions brought by another against the Company or Releasees. In the event that your assistance is requested or required in the pursuit of any claims brought against the Company or Releasees, you must provide written notice to the Company within five (5) business days of such request, unless requested by a governmental authority to the contrary.

Without additional compensation, you agree to cooperate reasonably with the Company and Releasees (including its and their outside counsel) in investigating, defending, prosecuting, litigating, filing, initiating, or asserting any actual or potential claims or other matters involving the Company and Releasees to the extent that the Company believes you may have relevant knowledge or information. You agree to make yourself available during and outside of regular business hours for such cooperation; *provided* that the Company shall not utilize this Section to require you to make yourself available to an

extent that would unreasonably interfere with your search for employment or any subsequent professional responsibilities that you may have. You agree to appear without the necessity of a subpoena to testify truthfully in any legal proceedings in which the Company calls you as a witness. In connection with fulfilling your obligations under this Section, your pre-approved, out of pocket and reasonable expenses will be reimbursed by the Company, which shall not include any attorneys' fees except as provided by the Company's by-laws and/or any applicable liability insurance policies.

7. Return of Company Property. You shall not dispose of any property of the Company including, without limitation, information or documents (including, without limitation, computerized data and any copies made of any computerized data or software) (all of the foregoing are collectively referred to as the "Documents") without the prior written authorization of the Company. On or before the Separation Date, as requested by the Company, you shall return to the Company all property of the Company, including, without limitation, computer equipment, electronic devices, iPads, iPhones, cellular phones and other mobile devices, software, keys and access cards, credit cards, files and any Documents containing information concerning the Company, its business or business relationships (in the latter two cases, actual or prospective). After returning all Documents and property of the Company, you shall delete and purge any duplicates of files or documents that may contain Company information from any non-Company computer or other device that remains your property. In the event that you discover that you continue to retain any such property, you shall return it to the Company or destroy it (in the case of computerized data and software already in the possession of the Company) immediately. For the avoidance of doubt, you may maintain copies of your own personnel records, to the extent applicable.

8. Non-disparagement.

(a) Subject to Section 9, you agree not to make any disparaging, critical or detrimental statements concerning the Company or any of its affiliates; its or their products or services provided or to be provided; its or their current or former officers, directors, stockholders, members, employees, managers or agents; and its or their business affairs or financial condition. You further agree not to take any actions or conduct yourself in any way that would reasonably be expected to affect adversely the reputation or goodwill of the Company or its affiliates; or its or their products or services provided or to be provided; or its or their current or former officers, directors, stockholders, members, employees, managers or agents. This non-disparagement obligation shall not in any way affect your obligation to testify truthfully in any legal proceeding.

(b) The Company will instruct each of the members of the Company's Executive Committee not to make any disparaging or detrimental statements concerning your employment with the Company or take any actions or conduct themselves in any way that would reasonably be expected to affect adversely your professional or personal reputation. This non-disparagement obligation shall not in any way affect any executive officer's obligation to testify truthfully in any legal proceeding.

9. Protected Disclosures. Nothing contained in this Agreement or the Other Agreements (including, without limitation, the Restrictive Covenants Agreement) limits your ability to file a charge or complaint with any federal, state or local governmental agency or commission (a "Government Agency"). In addition, nothing contained in this Agreement limits your ability to communicate with any Government Agency or otherwise participate in any investigation or proceeding that may be conducted by any Government Agency, nor does anything contained in this Agreement apply to truthful testimony in litigation. If you file any charge or complaint with any Government Agency and if the Government Agency pursues any claim on your behalf, or if any other third party pursues any claim on your behalf, you waive any right to monetary or other individualized relief (either individually or as part of any

collective or class action); *provided however* that nothing in this Agreement limits any right you may have to receive a whistleblower award or bounty for information provided to the Securities and Exchange Commission. Nothing in this Agreement or the Other Agreements (including, without limitation, the Restrictive Covenants Agreement) is intended to conflict with 18 U.S.C. § 1833(b), which provides that: “An individual shall not be held criminally or civilly liable under any Federal or State trade secret law for the disclosure of a trade secret that (A) is made (i) in confidence to a Federal, State, or local government official, either directly or indirectly, or to an attorney; and (ii) solely for the purpose of reporting or investigating a suspected violation of law; or (B) is made in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal.”

10. Communications Regarding Separation. You agree that you will not (without the prior written approval of the Company) communicate about your transition or separation with anyone until after the Company has made a formal written announcement about your transition and separation (the “Company Announcement”); provided that you may communicate with your tax advisors, attorneys, and family members about your transition and separation before the Company Announcement; provided further that you first advise such persons not to reveal information about your transition and separation and each such person agrees. Once the Company has announced your transition and separation, you agree to limit any communications regarding your transition and separation departure to statements that are consistent with the Company Announcement.

11. Section 409A.

(a) Anything in this Agreement to the contrary notwithstanding, if at the time of your separation from service within the meaning of Section 409A of the Internal Revenue Code of 1986, as amended (the “Code”), you are a “specified employee” within the meaning of Section 409A(a)(2)(B)(i) of the Code, then to the extent any payment or benefit that you become entitled to under this Agreement on account of your separation from service would be considered deferred compensation otherwise subject to the twenty percent (20%) additional tax imposed pursuant to Section 409A(a) of the Code as a result of the application of Section 409A(a)(2)(B)(i) of the Code, such payment shall not be payable and such benefit shall not be provided until the date that is the earlier of (A) six months and one day after your separation from service, or (B) your death. If any such delayed cash payment is otherwise payable on an installment basis, the first payment shall include a catch-up payment covering amounts that would otherwise have been paid during the six-month period but for the application of this provision, and the balance of the installments shall be payable in accordance with their original schedule.

(b) All in-kind benefits provided and expenses eligible for reimbursement under this Agreement shall be provided by the Company or incurred by you during the time periods set forth in this Agreement. All reimbursements shall be paid as soon as administratively practicable, but in no event shall any reimbursement be paid after the last day of the taxable year following the taxable year in which the expense was incurred. The amount of in-kind benefits provided or reimbursable expenses incurred in one taxable year shall not affect the in-kind benefits to be provided or the expenses eligible for reimbursement in any other taxable year (except for any lifetime or other aggregate limitation applicable to medical expenses). Such right to reimbursement or in-kind benefits is not subject to liquidation or exchange for another benefit.

(c) To the extent that any payment or benefit described in this Agreement constitutes “non-qualified deferred compensation” under Section 409A of the Code, and to the extent that such payment or benefit is payable upon your termination of employment, then such payments or benefits shall be payable only upon your “separation from service.” The determination of whether and when a

separation from service has occurred shall be made in accordance with the presumptions set forth in Treasury Regulation Section 1.409A-1(h).

(d) The parties intend that this Agreement will be administered in accordance with Section 409A of the Code. To the extent that any provision of this Agreement is ambiguous as to its compliance with Section 409A of the Code, the provision shall be read in such a manner so that all payments hereunder comply with, or are exempt from, Section 409A of the Code. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2). The parties agree that this Agreement may be amended, as reasonably requested by either party, and as may be necessary to fully comply with, or be exempt from, Section 409A of the Code and all related rules and regulations in order to preserve the payments and benefits provided hereunder without additional cost to either party.

(e) The Company makes no representation or warranty and shall have no liability to you or any other person if any provisions of this Agreement are determined to constitute deferred compensation subject to Section 409A of the Code but do not satisfy an exemption from, or the conditions of, such Section.

12. Tax Treatment. The Company shall undertake to make deductions, withholdings and tax reports with respect to payments and benefits under this Agreement to the extent that it reasonably and in good faith determines that it is required to make such deductions, withholdings and tax reports. Payments under this Agreement are stated in gross amounts and shall be paid in amounts net of any such deductions or withholdings. Nothing in this Agreement shall be construed to require the Company to make any payments to compensate you for any adverse tax effect associated with any payments or benefits or for any deduction or withholding from any payment or benefit.

13. Effect of Breach. In the event that you fail to comply with any of your obligations under this Agreement (including the obligations under the Other Agreements and the Restrictive Covenants Agreement), in addition to any other legal or equitable remedies it may have for such breach, including for damages and equitable relief, the Company shall have the right to (i) if you are still employed, end your employment for Cause, (ii) terminate its payments to you under the Agreement; and/or (iii) seek recovery of any payments made to you or for your benefit pursuant to this Agreement. Any such consequences of a breach by you will not affect the release or your continuing obligations under this Agreement, under the Other Agreements, under the Consulting Agreement or under the Restrictive Covenants Agreement.

14. Non-admission. This Agreement shall not be construed as an admission of any liability by the Company or you of any act of wrongdoing. Each of the Company and you specifically disclaims that the Company or any of its representatives has engaged in any wrongdoing or has taken any action that would be the basis for any finding of liability.

15. Legally Binding. You are advised to consult with an attorney before executing this Agreement. Once effective, this Agreement is a legally binding document and your signature will commit you to its terms. You acknowledge that you have been advised to discuss all aspects of this Agreement with your attorney, that you have carefully read and fully understand all of the provisions of this Agreement, and that you are voluntarily entering into this Agreement.

16. Absence of Reliance. In signing this Agreement, you are not relying upon any promises or representations made by anyone at or on behalf of the Company.

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17. Enforceability. Except for the General Release of Claims in Section 5, if any portion or provision of this Agreement (including, without limitation, any portion or provision of any section of this Agreement, or of the Restrictive Covenants Agreement or the Consulting Agreement) shall to any extent be declared illegal or unenforceable by a court of competent jurisdiction, then the remainder of this Agreement, or the application of such portion or provision in circumstances other than those as to which it is so declared illegal or unenforceable, shall not be affected thereby, and each portion and provision of this Agreement shall be valid and enforceable to the fullest extent permitted by law. If the General Release of Claims in Section 5 is found to be invalid or unenforceable in whole or in part, the Company will have the option in its sole discretion either to sever the invalid or unenforceable portion and enforce the rest of the Agreement, or to cancel the entire Agreement. In the event the Company exercises such option to cancel the entire Agreement, the Agreement shall be null and void and none of the benefits set forth in Section 3 shall be owing, paid, or provided, and if such amounts or benefits have been paid or provided, you shall repay to the Company the total gross amount or value of any such benefits already paid or provided, and the total gross amount of the amounts otherwise being waived in Section 3.

18. Waiver; Amendment. No waiver of any provision of this Agreement shall be effective unless made in writing and signed by the waiving party. The failure of any party to require the performance of any term or obligation of this Agreement, or the waiver by any party of any breach of this Agreement, shall not prevent any subsequent enforcement of such term or obligation or be deemed a waiver of any subsequent breach. This Agreement may not be modified or amended except in a writing signed by both you and a duly authorized officer of the Company.

19. Forum; Equitable Relief.

(a) You and the Company hereby agree that the Superior Court of the Commonwealth of Massachusetts and the United States District Court for the District of Massachusetts shall have the exclusive jurisdiction to consider any matters related to this Agreement, including without limitation any claim for violation of this Agreement. With respect to any such court action, you (i) submit to the jurisdiction of such courts, (ii) consent to service of process, and (iii) waive any other requirement (whether imposed by statute, rule of court or otherwise) with respect to personal jurisdiction or venue.

(b) You agree that it would be difficult to measure any harm caused to the Company that might result from any breach by you of your promises set forth in this Agreement and that in any event money damages would be an inadequate remedy for any such breach. Accordingly, you agree that if you breach, or propose to breach, any portion of your obligations under this Agreement, the Company shall be entitled, in addition to all other remedies it may have, to an injunction or other appropriate equitable relief to restrain any such breach, without showing or proving any actual damage to the Company and without the necessity of posting a bond.

20. Governing Law; Construction of Agreement. This Agreement shall be construed and governed in accordance with the substantive laws of the Commonwealth of Massachusetts, without giving effect to any choice or conflict of law provision or rule (whether of the Commonwealth of Massachusetts or any other jurisdiction) that would cause the application of laws of any jurisdictions other than those of the Commonwealth of Massachusetts. The parties acknowledge and agree that this Agreement shall not be construed more strictly against one party than another party merely by virtue of the fact that it, or any part of it, may have been prepared by counsel for one of the parties, it being recognized that it is the result of arms-length negotiations between the parties and all parties have contributed substantially and materially to the preparation of this Agreement. The headings contained in this Agreement are for

reference purposes only and shall not affect in any way the meaning or interpretation of this Agreement. References to agreements and other documents shall be deemed to include all subsequent amendments and other modifications thereto. References to statutes shall include all regulations promulgated thereunder and references to statutes or regulations shall be construed as including all statutory and regulatory provisions consolidating, amending or replacing the statute or regulation.

21. Entire Agreement. This Agreement constitutes the entire agreement between you and the Company and supersedes any previous agreements or understandings between you and the Company, including that certain offer letter by and between the Company and you dated as of December 28, 2020, *provided however* that the Severance Plan, Indemnification Agreement, Restrictive Covenants Agreement, Other Agreements and Equity Documents shall remain in full force and effect and further provided that, if you meet the Conditions set forth in Section 2 of this Agreement and the parties enter into the Consulting Agreement, then this Agreement and the Consulting Agreement together will supersede any previous agreements or understandings between you and the Company.

22. Time for Consideration; Agreement Effective Date. You understand and acknowledge that you have been given the opportunity to consider this Agreement for 21 calendar days from your receipt of this Agreement before signing it (the “Agreement Consideration Period”). Any changes to this Agreement, material or otherwise, will not restart the running of the Agreement Consideration Period. In signing this Agreement, you acknowledge that you have knowingly and voluntarily entered into this Agreement without any duress or undue influence on the part or behalf of the parties hereto or any affiliate thereof. You acknowledge that your release of Claims is knowing and voluntary, including without implication of limitation your release of claims of age discrimination under the Age Discrimination in Employment Act, 29 U.S.C. § 621 et seq. To accept this Agreement, you must return a signed, unmodified original or PDF copy of this Agreement so that it is received by the undersigned at or before the expiration of the Agreement Consideration Period. If you sign this Agreement before the end of the Agreement Consideration Period, you acknowledge by signing this Agreement that such decision was entirely voluntary and that you had the opportunity to consider this Agreement for the entire Agreement Consideration Period. You have seven (7) business days following your execution of this Agreement to revoke the Agreement by written notice to the undersigned (such seven (7) business day period, the “Agreement Revocation Period”). For such a revocation to be effective, it must be delivered so that it is received by the Company at or before the expiration of the Agreement Revocation Period. This Agreement shall not become effective or enforceable during the Agreement Revocation Period. This Agreement shall become effective as of the first (1st) day after the expiration of the Agreement Revocation Period, *provided* that the Company has also executed this Agreement by that date (the “Agreement Effective Date.”) For the avoidance of doubt, if you do not enter into this Agreement, your employment will end but you will not be entitled to any of the Severance Benefits set forth in this Agreement.

23. Counterparts. This Agreement may be executed in counterparts, each of which shall be considered an original and all of which shall constitute one agreement. The signature of each party may be delivered by facsimile or by scanned image (e.g., .pdf or .tiff file extension name) as an attachment to electronic mail (e-mail), and such facsimile or scanned signature shall be treated in all respects as having the same effect as an original inked signature.

[Remainder of Page Intentionally Left Blank]

Please indicate your agreement to the terms of this Agreement by signing and returning this letter to me within the time period set forth above.

Very truly yours,
/s/ Tracey Franklin
Tracey Franklin
Chief Human Resources Officer

The foregoing is agreed to and accepted by:

/s/ Corinne Le Goff
Signature

Corinne Le Goff
Employee Name

11/11/2021
Date

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Exhibit A
Restrictive Covenants Agreement

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Exhibit B
Consulting Agreement

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (together with the attached Appendix A, B and C, the "Agreement"), is made by and between ModernaTX, Inc., a Delaware corporation having a place of business at 200 Technology Square, Cambridge, MA 02139, USA ("Moderna"), and Corinne Le Goff, an individual residing at [***] ("Consultant"). This Agreement shall become effective on the last day of Consultant's employment with the Company (such actual last day of employment, the "Effective Date"), and as agreed to in the Executive Separation and Transitional Services Agreement (the "Executive Separation Agreement") to which this Agreement is attached as Exhibit A; provided that this Agreement shall be *void ab initio* if Consultant does not enter into the Executive Separation Agreement or satisfy each of the Conditions (as defined in the Executive Separation Agreement). Moderna desires to have the benefit of Consultant's knowledge and experience, and Consultant desires to provide services to Moderna, all as provided in this Agreement. Moderna and Consultant may be referred to herein individually as a "Party" and collectively as the "Parties."

1. **Services.** During the Term (as defined below), Moderna or its Affiliates (as defined below) may from time to time request, and Consultant agrees to provide, consulting and advisory services related to Commercial operations and strategy (the "Services") and certain deliverables ("Deliverables") to Moderna and its Affiliates in accordance with the terms attached hereto as Appendix A, which Appendix A is hereby incorporated herein by reference. Consultant will deliver all Deliverables to Moderna in the form specified, and on the schedule set forth, in Appendix A. Any changes to the Services or Deliverables must be agreed to in writing between Consultant and Moderna prior to implementation of the changes. Subject to compliance with Consultant's obligations in this Agreement, Consultant shall retain the sole control and discretion to determine the methods by which Consultant performs the Services. As used herein, "Affiliate" means, with respect to an entity, any other entity that directly, or indirectly through one or more intermediaries, controls, is controlled by or is under common control with such first entity, with "control" meaning the power to direct the management or policies of an entity, whether through ownership of voting securities or by contract relating to voting rights or corporate governance, resolution, regulation or otherwise.
2. **Performance.** Consultant agrees to provide the Services in accordance with all applicable laws and regulations, prevailing high-level professional standards and the additional applicable terms and policies set forth in Appendix B. Consultant will provide Services not to exceed twenty percent (20%) of the average level of services provided by Consultant as an employee of the Company prior to the Separation Date (as defined in the Executive Separation Agreement).
3. **Independent Contractor Relationship.** The Parties understand and agree that Consultant is an independent contractor and not an agent or employee of Moderna or its Affiliates. Consultant has no authority to obligate Moderna or its Affiliates by contract or otherwise. Consultant will not be eligible for any employee benefits of Moderna or its Affiliates and expressly waives any rights to any employee benefits. Consultant will bear sole responsibility for paying and reporting Consultant's own applicable federal and state income taxes, social security taxes, unemployment insurance, workers' compensation, health or disability insurance, retirement benefits, and other welfare or pension benefits, if any, and Consultant indemnifies and holds Moderna harmless from and against any liability with respect to such taxes, benefits and other matters.
4. **Compensation.** As full consideration for the performance of the Services and delivery of the Deliverables, Consultant shall continue to vest during the Term (as defined in Section 8 hereof) in (a) the non-qualified stock option to purchase 58,563 shares of the Company's common stock that he was granted on February 1, 2021 (the "2021 Option"); and (b) the award of 25,400 restricted units granted on February 1, 2021 (the "2021 RSUs"), and subject in each case ((a) through (b)) to

the terms of (i) the Moderna, Inc. 2018 Stock Option and Incentive Plan (the “Plan”); (ii) the applicable Non-Qualified Stock Option Grant Notice; (iii) the applicable Non-Qualified Stock Option Agreement; and (iv) the applicable Restricted Stock Unit Award Agreement ((i) through (iv) collectively, the “Equity Documents”). Consultant shall cease vesting in the 2021 Option and the 2021 RSUs on the last day of the Term and may exercise any vested portion of the 2021 Option in accordance with the terms of the Equity Documents and subject to the time limits on exercisability. Moderna also agrees to reimburse Consultant the expenses as expressly set forth in Appendix A.

5. **Restrictive Covenants.** Consultant acknowledges and agrees that the terms of the Employee Confidentiality, Assignment, Nonsolicitation and Noncompetition Agreement by and between Consultant and the Company, dated as of December 29, 2020, a copy of which is attached hereto as Appendix C (as amended by the Executive Separation Agreement, the “Restrictive Covenants Agreement”), shall apply during the Term and thereafter in accordance with its terms. The non-competition and non-solicitation restrictions contained in the Restrictive Covenants Agreement apply “[d]uring the period in which you perform services for or at the request of the Company [ModernaTX, Inc., or any present or future direct or indirect parent, subsidiary or affiliate thereof] and for one (1) year following the termination of your provision of services to the Company for any reason or for no reason.” Accordingly, for the avoidance of doubt, the non-competition and non-solicitation restrictions shall apply during the Term and for the one (1) year period following the last day of the Term. The other obligations in the Restrictive Covenants Agreement shall apply during the Term and thereafter, in accordance with their terms.
6. **Compliance with Obligations to Third Parties.** Consultant represents and warrants to Moderna that the terms of this Agreement, Consultant’s performance of the Services under the Agreement and Consultant’s acceptance of related compensation do not and will not conflict with any of Consultant’s obligations to any third parties. Consultant agrees not to use any trade secrets or other confidential information of any other person, firm, corporation, institution or other third party in connection with any of the Services. If Consultant is an employee of or consultant or advisor to another company or institution or an affiliate of any foreign, federal or state government, facility, university or institution, Consultant represents and warrants that Consultant is not prohibited by any applicable laws, regulations, policies (including policies concerning professional consulting, non-competition, and additional workload), procedures, or ethical guidelines from fulfilling any of Consultant’s obligations or responsibilities pursuant to this Agreement or from accepting compensation under this Agreement. Consultant agrees not to make any use of any funds, space, personnel, facilities, equipment or other resources of a third party in performing the Services and agrees not to take any other action that would result in a third party asserting ownership of, or other rights in, any Inventions (as defined in the Restrictive Covenants Agreement), unless agreed upon in writing in advance by Moderna.
7. **Publicity.** Consultant shall not use the name or any trademark (or adaptation thereof) of Moderna or any of its Affiliates for any marketing purposes or other uses without Moderna’s prior written consent.
8. **Expiration/Termination.** The term of this Agreement (the “Term”) will commence on the Effective Date and expire on February 3, 2022, unless sooner terminated pursuant to the provisions of this Section 8. Moderna may terminate this Agreement at any time for Cause (as defined below) upon at least three (3) days’ written notice to Consultant. Any such termination for Cause shall become effective within three (3) business days of delivery of the notice, unless the circumstances giving rise to the for Cause termination are cured within such three (3) business days. For purposes of this Agreement, “Cause” shall mean (i) Consultant’s refusal to perform requested Services under this Agreement, or (ii) a material breach by Consultant of this

Agreement, the Restrictive Covenants Agreement or the Executive Separation Agreement. Consultant may terminate this Agreement for any reason upon not less than fourteen (14) days' prior written notice to Moderna. Any expiration or termination of this Agreement shall be without prejudice to any obligation of either Party that has accrued prior to the effective date of expiration or termination. Upon expiration or termination of this Agreement, neither Consultant nor Moderna will have any further obligations under this Agreement, except that (a) Consultant will terminate all Services in progress in an orderly manner as soon as practicable and in accordance with a schedule agreed to by Moderna, unless Moderna specifies in the notice of termination that Services in progress should not be completed; (b) Consultant will deliver to Moderna all Deliverables made through expiration or termination; (c) Consultant will immediately return to Moderna all Moderna property and other Confidential Information (as defined in the Restrictive Covenants Agreement) and copies thereof provided to Consultant under this Agreement; and (d) the terms, conditions and obligations under Sections 3, 5 through 8, 10, and relevant portions of Section 12 will survive expiration or termination of this Agreement.

9. **Warranties and Additional Covenants.** Consultant represents, warrants and covenants that: (a) Consultant has the full power and authority to enter into and perform the Services pursuant to this Agreement, without the need for any consents or approvals not yet obtained; (b) Consultant has the right to grant the rights and assignments granted herein, without the need for any assignments, releases, consents, approvals or other rights not yet obtained; (c) the Services, including any Deliverables required hereunder, shall be free from material errors or other defects; (d) the execution of this Agreement by Consultant and Consultant's performance hereunder will not violate or be a breach of any agreement or obligation with any other person or entity.
10. **Indemnification.** Moderna shall indemnify and hold harmless, and at Consultant's request, defend, Consultant from and against any and all third party claims, losses, liabilities, damages, settlements, expenses and costs (including attorneys' fees and costs) which arise out of or relate to (a) any breach (or claim or threat thereof that, if true, would be a breach) of this Agreement by Moderna, and (b) Moderna's products, including for claims arising out of the negligence or intentional wrongdoing of Moderna.
11. **Miscellaneous.**
 - (a) **Use of Name.** Consultant consents to the use by Moderna of Consultant's name on its website, in press releases, company brochures, offering documents, presentations, reports or other documents in printed or electronic form, and in any documents filed with or submitted to any governmental or regulatory agency or any securities exchange or listing entity.
 - (b) **Defend Trade Secrets Act.** 18 U.S.C. § 1833(b) provides: "An individual shall not be held criminally or civilly liable under any Federal or State trade secret law for the disclosure of a trade secret that (A) is made (i) in confidence to a Federal, State, or local government official, either directly or indirectly, or to an attorney; and (ii) solely for the purpose of reporting or investigating a suspected violation of law; or (B) is made in a complaint or other document filed in a lawsuit or other proceeding, if such filing is made under seal." Nothing in this Agreement is intended to conflict with 18 U.S.C. § 1833(b) or create liability for disclosures of trade secrets that are expressly permitted by 18 U.S.C. § 1833(b).
 - (c) **Protected Disclosures.** Nothing contained in this Agreement limits Consultant's ability to communicate with any federal, state or local governmental agency or commission, including to provide documents or other information, without notice to the Company.

- (d) **Entire Agreement; Counterparts.** This Agreement, together with Appendix A, Appendix B, and Appendix C, contains the entire agreement of the Parties with regard to its subject matter, and supersedes all prior or contemporaneous written or oral representations, agreements and understandings between the Parties relating to that subject matter; provided however, that the Executive Separation Agreement, the Indemnification Agreement as defined in the Executive Separation Agreement, the Equity Documents and the Restrictive Covenants Agreement shall remain in full force and effect. For the avoidance of doubt, the Indemnification Agreement between Consultant and the Company dated December 29, 2020, shall remain in full force and effect in accordance with its terms. This Agreement may be changed only by a writing signed by Consultant and an authorized representative of Moderna. This Agreement may be executed in any number of counterparts, each of which will be deemed an original.
- (e) **Assignment and Binding Effect.** The Services to be provided by Consultant are personal in nature. Consultant may not assign or transfer this Agreement or any of Consultant's rights or obligations hereunder without Moderna's prior written consent. In no event will Consultant assign or delegate responsibility for actual performance of the Services to any third party. Moderna may transfer or assign this Agreement without the prior written consent of Consultant. Any purported assignment or transfer in violation of this Section is void. This Agreement will be binding upon and inure to the benefit of the Parties and their respective legal representatives, heirs, successors and permitted assigns.
- (f) **Notices.** All notices required or permitted under this Agreement must be in writing and must be given by directing the notice to the address for the receiving Party set forth in this Agreement or at such other address as the receiving Party may specify in writing under this procedure. Notices to Moderna will be marked "Attention: Chief Legal Officer ("CLO")." All notices must be given (i) by personal delivery, with receipt acknowledged, (ii) by prepaid certified or registered mail, return receipt requested, (iii) by prepaid recognized next business day delivery service or 2-day international delivery service; or (iv) by email to Consultant's Moderna email address or, in the case of Moderna, to the CLO's email address. Notices will be effective upon receipt or at a later date stated in the notice.
- (g) **Governing Law.** This Agreement and any disputes relating to or arising out of this Agreement will be governed by, construed, and interpreted in accordance with the internal laws of the Commonwealth of Massachusetts, without regard to any choice of law principle that would require the application of the law of another jurisdiction. The Parties agree to submit to the exclusive jurisdiction of the state and federal courts located in Massachusetts and waive any defense of inconvenient forum to the maintenance of any action or proceeding in such courts.
- (h) **Severability; Reformation; Waiver.** Each provision in this Agreement is independent and severable from the others, and no provision will be rendered unenforceable because any other provision is found by a proper authority to be invalid or unenforceable in whole or in part. If any provision of this Agreement is found by such an authority to be invalid or unenforceable in whole or in part, such provision shall be changed and interpreted so as to best accomplish the objectives of such unenforceable or invalid provision and the intent of the Parties, within the limits of applicable law. Any delay in enforcing a Party's rights under this Agreement, or any waiver as to a particular default or other matter, will not constitute a waiver of such Party's rights to the future enforcement of its rights under this Agreement, except with respect to an express written waiver relating to a particular matter for a particular period of time signed by Consultant and an authorized representative of the waiving Party, as applicable

- (i) **Remedies.** Consultant agrees that (i) Moderna may be irreparably injured by a breach of this Agreement by Consultant; (ii) money damages would not be an adequate remedy for any such breach; (iii) as a remedy for any such breach Moderna will be entitled to seek equitable relief, including injunctive relief and specific performance, without being required by Consultant to prove actual damages or post bond; and (iv) such remedy will not be the exclusive remedy for any breach of this Agreement.
- (j) **Further Assurances.** Each Party shall duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things as may be necessary or as the other Party may reasonably request in connection with this Agreement or to carry out more effectively the provisions and purposes hereof, or to better assure and confirm unto such other Party its rights and remedies under this Agreement.
- (k) **Extension to Affiliates.** Moderna shall have the right to extend the rights, licenses, immunities and obligations granted or imposed in this Agreement to one or more of its Affiliates. All applicable terms and provisions of this Agreement shall apply to any such Affiliate to which this Agreement has been extended to the same extent as such terms and provisions apply to Moderna. Moderna shall remain fully liable for any acts or omissions, including financial liabilities, of such Affiliates. To the extent that this Agreement imposes obligations on any Affiliates of Moderna, Moderna agrees to cause its Affiliates to perform such obligations.
- (l) **Electronic Transmissions.** This Agreement may be transmitted in electronic format and shall not be denied legal effect solely because it was formed or transmitted, in whole or in part, by electronic record; however, this Agreement must then remain capable of being retained and accurately reproduced, from time to time, by electronic record by the Parties to this Agreement and all other persons or entities required by law. An electronically transmitted signature to this Agreement will be deemed an acceptable original for purposes of consummating this Agreement and binding the Party providing such electronic signature.
- (m) **Construction.** Whenever any provision of this Agreement uses the term “including” (or “includes”), such term will be deemed to mean “including without limitation” (or “includes without limitations”). “Herein,” “hereby,” “hereunder,” “hereof” and other equivalent words refer to this Agreement as an entirety and not solely to the particular portion of this Agreement in which any such word is used. Except where the context otherwise requires, whenever used, the singular will include the plural and the plural the singular.

[Signature page follows]

IN WITNESS WHEREOF, the Parties have executed this Consulting Agreement as of the Effective Date.

ModernaTX, Inc.

CONSULTANT

By: /s/ Tracey Franklin

/s/ Corinne Le Goff

Name: Tracey Franklin

Name: Corinne Le Goff

Title: Chief Human Resources Officer

Title: Consultant

{00036909.1}

Appendix A

**To the Consulting Agreement between
ModernaTX, Inc. and Corinne Le Goff**

1. **Services:**

Consultant will provide Services with respect to commercial operations and strategy, on a schedule and at a location or locations indicated above or as otherwise mutually agreed between Consultant and Moderna (or its Affiliate, if applicable). In addition, Consultant will be available for a reasonable number of telephone and/or written consultations.

2. **Deliverables:**

The Deliverables will relate to commercial operations and strategy and will be determined by the Company.

3. **Compensation:**

Equity Vesting: As explained in Section 4 above, Consultant shall continue to vest in the 2021 Option and the 2021 RSUs during the Term.

Expenses: Moderna will reimburse Consultant for any pre-approved expenses actually incurred by Consultant in connection with the provision of Services. Requests for reimbursement will be in a form reasonably acceptable to Moderna, will include supporting documentation and will accompany Consultant's invoices.

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Appendix B

Additional Applicable Terms and Policies

- A. Code of Business Ethics and Conduct of Moderna, Inc. (available at www.modernatx.com)
- B. Insider Trading Policy of Moderna, Inc., a copy of which has been provided to Consultant.

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Appendix C

Restrictive Covenants Agreement



March 4, 2021

Shannon Thyme Klinger [***]
[***]
[***]

Re: Employment Letter Agreement Between ModernaTX, Inc. and Shannon Klinger

Dear Shannon,

ModernaTX, Inc. (together with its affiliates, the "Company") is pleased to enter into this Employment Letter Agreement ("Agreement") regarding your employment as Chief Legal Officer, reporting to the Chief Executive Officer. You shall have all duties and authorities customary for such position. Your effective date of hire will be on or before June 1, 2021 (the "Start Date"), or another Start Date mutually agreed upon by you and the Company, and you will perform services for the Company as a regular, full-time employee. The initial terms of your employment are set forth below.

You agree to devote your full business time to the performance of your duties, and not engage in any other business activity without the approval of the CEO. Notwithstanding the foregoing, you will be permitted to manage your personal investments, engage in civic and charitable activities, and serve on boards and engage in other activities as are approved by the CEO from time to time, which approval shall not be unreasonably withheld or delayed, provided that such activities do not interfere with the performance of your duties, create a conflict of interest or violate any agreement with the Company.

Your initial base salary will be at the rate of \$650,000.00 (USD) per year. All wages will be paid in accordance with the Company's normal biweekly pay schedule for salaried employees. Your base salary will be subject to periodic review for potential adjustment at the Company's discretion, and any such adjustments shall thereafter constitute your Base Salary for all purposes under this Agreement and related agreements or plans. Downward adjustments in your Base Salary, if any, will only be made in a manner that is consistent with the rest of the executive team and at the direction of the Board of Directors (and shall otherwise be subject to your rights under the Amended and Restated Executive Severance Plan ("ESP").

In addition to the foregoing, upon your commencement of employment with the Company, you will be paid a one-time signing bonus of \$250,000.00 less applicable taxes (the "Signing Bonus"). You acknowledge and agree that you will repay a pro-rated portion of the Signing Bonus to the Company within 10 days of your last day of employment if you voluntarily terminate your employment with the Company not following the occurrence of Good Reason or your employment is terminated for Cause by the Company (as such terms are defined and otherwise pursuant to the terms of, the ESP in effect as of the date of this Agreement) during the first 24 months of your employment. That amount may be collected by the Company, unless prohibited by applicable law, either directly or indirectly, from any (i) payment of any kind due to you from the Company or any affiliate thereof including, without limitation, accrued wages, vacation, final wages, and expense reimbursements to the fullest extent permitted by applicable law; and/or (ii) the forfeiture or cancellation of any equity interest owned by you in the Company or any subsidiary or affiliate thereof, whether now existing or hereafter formed, and regardless of the form such equity interest (e.g., common units, incentive units (also referred to as profits interests), options to acquire common units or otherwise).

You will be eligible to earn an annual performance bonus. The Company will initially target the bonus at 60% of your Base Salary (prorated based on your Start Date, provided that your Start Date is on or before the first Monday of October of the applicable calendar year). If your Start Date is after the first Monday of October, you will not be eligible for a bonus for the calendar year in which you were hired. The actual bonus percentage earned will be subject to the Company's assessment of individual and Company performance based upon established criteria, and otherwise pursuant to the Senior Executive Cash Incentive Bonus Plan. The bonus, if any, will be paid no later than March 15 of the calendar year following the calendar year to which such bonus relates. Except as otherwise provided herein, including under the terms of the ESP, you must be employed on the date a bonus is paid to receive that bonus.

Within thirty (30) days of your Start Date, you shall be granted, pursuant to Moderna's equity incentive program an equity award equivalent to a total value of \$8,000,000.00 as of the grant date (such equity award is referred to as the "New Hire Equity Award"). The New Hire Equity Award will vest according to the following schedule: 25% of the New Hire Equity Award will vest on the first anniversary of the date that the equity is granted to you which is set as the first Monday of each month on a consistent basis for all new employees at Moderna (the Grant Date), and the remaining 75% of the New Hire Equity Award will vest in equal calendar quarterly installments over the next three (3) years, provided that, in each case, except as otherwise provided herein, you continue to provide continuous services to the Company as of each such vesting date. The New Hire Equity Award is subject to our "Your Equity Selection" (YES) program. You may choose to have your award delivered to you in one of the following mixes of Non-Qualified Stock Options and/or Restricted Stock Units:

- 100% of the value delivered in the form of Non-Qualified Stock Options.
- 75% of the value delivered in the form of Non-Qualified Stock Options and 25% in value delivered in the form of Restricted Stock Units. This is the default choice if no selection is made.
- 50% of the value delivered in the form of Non-Qualified Stock Options and 50% in value delivered in the form of Restricted Stock Units.

You will receive an email from the Compensation Team at the Company to register your selection prior to your grant date. In the event of a stock split, stock consolidation or similar event prior to the grant of the New Hire Equity Award, the number of shares subject thereto shall be adjusted proportionately. The grant price of the New Hire Equity Award will be equal to the closing price on the Grant Date. The grant of the New Hire Equity Award will be conditioned upon your execution of all necessary documentation relating to the New Hire Equity Award as determined by the Company (all such documentation is collectively referred to as the "New Hire Equity Award Documentation"). The New Hire Equity Award will be subject to the terms and conditions set forth in the New Hire Equity Award Documentation.

In addition to the New Hire Equity Award within thirty (30) days of your Start Date, you shall also be granted an equity award equivalent to a total value of \$2,000,000.00 as of the Grant Date (such equity award is referred to as the "Special Equity Award"), which shall be delivered in the form of Restricted Stock Units. The Special Equity Award will vest on the following schedule: 100% of the Special Equity Award will vest on the third anniversary of the Grant Date, provided that, except as otherwise provided herein, you continue to provide continuous services to the Company as of such vesting date.

In the event of a stock split, stock consolidation or similar event prior to the grant of the New Hire Equity Award or the Special Equity Award (collectively, the "Initial Awards"), the number of shares subject thereto shall be adjusted proportionately. The grant price of the Initial Awards will be equal to the closing price on the day of grant. The grant of these awards will be conditioned upon, your execution of all necessary documentation relating to the awards as determined by the Company (all such documentation is collectively referred to as the "New Hire Equity Award Documentation"). The Initial Awards will be subject to the terms and conditions set forth in the New Hire Equity Award Documentation. The forms of your New Hire Equity Award Documentation are attached hereto.

For avoidance of doubt, all accelerated/continued equity vesting and/or payment provisions provided to executives generally regarding equity awards, whether pursuant to the ESP, the Moderna, Inc. 2018 Stock Option and Incentive Plan ("Incentive Plan"), or otherwise, shall apply to your Initial Awards.

Further, subject to the Incentive Plan and provided your Start Date is on or before the first Monday of October of the applicable calendar year, you will be eligible to receive an additional annual equity award related to your performance for the eligible performance period (the "Annual Equity Award"). Annual Equity Awards typically will be issued in the first quarter of the year following the performance period. Your annual grants will be based on a combination of market data and performance. You will receive an annual grant that will be a mix of stock options, RSU's, and potentially PSU's subject to the current executive pay policies in place. The target value of your Annual Equity Award is \$3,500,000.00. Your first Annual Equity Award will be pro-rated based upon your Start Date. Annual equity guidelines are subject to change and may be updated based on market conditions. Your Annual Equity Awards shall contain such terms and conditions (other than amounts), including but not limited to vesting schedule and treatment incident to a Sale Event and/or Termination, substantially similar to those generally provided to other members of the executive committee other than the CEO.

You may be required to relocate to the Greater Boston area, as applicable, by June 1, 2021, or as mutually agreed upon by both parties. Your principal place of employment shall be Cambridge, MA, except to the extent that remote work arrangements are necessitated by the Covid-19 pandemic. The Company will pay reasonable costs associated with your relocation (the "Relocation Expenses") in accordance with the Employee Relocation Guidelines ("Guidelines") that are in effect at the time of the initiation of your relocation case. Notwithstanding the foregoing and any terms or limitations in such Guidelines, however, the Company agrees to provide and pay (i) without regard to volume/weight, the costs of shipping and storage (for up to six (6) months) of your household goods and personal effects; (ii) the costs of temporary housing for you and your family for up to three (3) months; (iii) the costs of any amounts you are required to pay incident to early termination of your current residential lease; (iv) business class airfare for any travel incident to such relocation. In addition to the foregoing, you shall also receive a one-time Relocation Allowance of \$25,000. The Company will determine in its reasonable judgment what portion, if any, of your Relocation Expenses are for nondeductible expenses in accordance with applicable law and will comply with associated withholding and tax reporting obligations. You acknowledge and agree that you will repay a pro-rated portion of the Relocation Expenses to the Company within 10 days of your last day of employment if you voluntarily terminate your employment with the Company not following an occurrence of Good Reason or your employment is terminated for Cause within 24 months of the initiation of your relocation case. That amount may be collected by the Company, unless prohibited by applicable law, either directly or indirectly, from any (i) payment of any kind due to you from the Company or any affiliate thereof including, without limitation, accrued wages, vacation, final wages, and expense reimbursements to the fullest extent permitted by applicable law; and/or (ii) the forfeiture or cancellation of any equity interest owned by you in the Company or any subsidiary or affiliate thereof, whether now existing or hereafter formed, and regardless of the form such equity interest (e.g., common units, incentive units (also referred to as profits interests), options to acquire common units or otherwise).

In addition to your compensation, you may take advantage of various benefits offered by the Company from time to time, subject to any eligibility requirements. Currently the Company provides group medical and dental insurance, short term disability coverage, group life insurance and a 401(k) plan. These benefits, of course, may be modified, changed or eliminated from time to time at the sole discretion of the Company, and the provision of such benefits to you in no way changes or impacts your status as an at-will employee. Where a particular benefit is subject to a formal plan (for example, medical insurance or life insurance), eligibility to participate in and receive any particular benefit is governed solely by the applicable plan document. Notwithstanding the foregoing, the Company agrees that you shall be entitled to a minimum of four (4) weeks annual paid vacation one of which will be the Company's annual shutdown if the Company determines in any year to have a shutdown. Should you ever have any questions about Company benefits, you should ask for a copy of the applicable plan document. You will also be eligible for any additional vacation pursuant to the Company's policies in effect from time to time.

You shall also be provided a Moderna, Inc. Officer's Indemnification Agreement, which shall be in addition to any rights of indemnification and to receive advancement to which you may be entitled under applicable law, Moderna's organizing documents, any agreement, a vote of stockholders or a resolution of directors, or otherwise.

All forms of compensation referred to in this Agreement are subject to reduction to reflect applicable withholding and payroll taxes and other deductions required by law.

You acknowledge and agree that employment with the Company is "at will." You are not being offered employment for a definite period of time, and either you or the Company may terminate the employment relationship at any time and for any reason without prior notice, subject to and in accordance with the terms and conditions of the ESP and other executive plans that may be applicable to you from time to time. Although your job duties, title, reporting structure, compensation and benefits, as well as the Company's personnel policies and procedures, may change prospectively from time to time, subject to your severance and termination rights in the ESP or any successor severance agreement or plan, the "at-will" nature of your employment may only be changed by a written agreement signed by you and the Chief Executive Officer, which expressly states the intention to modify the at-will term of your employment.

The Company acknowledges and agrees that you shall be a Participant in the current ESP upon your Start Date. A copy of the Participation Letter to the ESP is attached.

Further, for the avoidance of doubt, if the Company fails to employ you on the Start Date, you shall be entitled to: (i) all of the termination payments, treatment and benefits set forth in the ESP as if you were already a Participant on the day before you were notified of such failure; (ii) payment of the Hiring Bonus and Relocation Expenses as set forth above.

As a condition of the commencement of your employment, you are required to enter into an Employee Confidentiality, Assignment, Nonsolicitation and Noncompetition Agreement (the "Restrictive Covenants Agreement"), a copy of which is enclosed with this Agreement. You also, represent that, based on your reasonable and good faith belief, you are not subject to any confidentiality, non-competition agreement or any other similar type of restriction that may affect your ability to devote full time and attention to your work at the Company, and have disclosed any applicable agreements to the Company. You further represent that you have not used and will not use or disclose any trade secret or other proprietary right of any previous employer or any other party.

The Immigration Reform and Control Act requires employers to verify the employment eligibility and identity of new employees. You will receive a Form I-9 that you will be required to complete. Please bring the appropriate documents listed on that form with you when you report for work. We will not be able to employ you if you fail to comply with this requirement.

This Agreement (including the documents references herein, e.g. the ESP, the New Hire Equity Award Documentation, the Incentive Plan, the Senior Executive Cash Incentive Bonus Plan, the Guidelines the Participation Agreement, the Indemnification Agreement and the enclosed Restrictive Covenants Agreement constitute the complete agreement between you and the Company, contain all of the terms of your employment with the Company and supersede any prior agreements, representations or understandings (whether written, oral or implied) between you and the Company.

Shannon, we look forward to your joining the Company and are pleased that you will be working with us to build a transformative company for patients.

Very truly yours, MODERNATX, INC.
/s/ Tracey Franklin

By: Tracey Franklin
Title: Chief Human Resources Officer

Accepted and Agreed:

Shannon Thyme Klinger

/s/ Shannon Thyme Klinger

3/5/2021

Date

**RESTRICTED STOCK UNIT AWARD AGREEMENT
FOR COMPANY EMPLOYEES
UNDER THE MODERNA, INC.
2018 STOCK OPTION AND INCENTIVE PLAN**

Name of Grantee: **[Participant Name]**

No. of Restricted Stock Units: **[Number of Shares Granted]**

Grant Date: **[Grant date]**

Pursuant to the Moderna, Inc. 2018 Stock Option and Incentive Plan as amended through the date hereof (the "Plan"), Moderna, Inc. (the "Company") hereby grants an award of the number of Restricted Stock Units listed above (an "Award") to the Grantee named above. Each Restricted Stock Unit shall relate to one share of Common Stock, par value \$0.0001 per share (the "Stock") of the Company.

1. Restrictions on Transfer of Award. This Award may not be sold, transferred, pledged, assigned or otherwise encumbered or disposed of by the Grantee, and any shares of Stock issuable with respect to the Award may not be sold, transferred, pledged, assigned or otherwise encumbered or disposed of until (i) the Restricted Stock Units have vested as provided in Paragraph 2 of this Agreement and (ii) shares of Stock have been issued to the Grantee in accordance with the terms of the Plan and this Agreement.

2. Vesting of Restricted Stock Units. The restrictions and conditions of Paragraph 1 of this Agreement shall lapse on the Vesting Date or Dates specified in the vesting schedule attached as Appendix A to this Agreement so long as the Grantee continues to have a Service Relationship with the Company or a Subsidiary on such Dates. If a series of Vesting Dates is specified, then the restrictions and conditions in Paragraph 1 shall lapse only with respect to the number of Restricted Stock Units specified as vested on such date.

The Administrator may at any time accelerate the vesting schedule specified in this Paragraph 2.

3. Termination of Service Relationship. If the Grantee's Service Relationship with the Company or a Subsidiary terminates for any reason (other than death or permanent disability) prior to the satisfaction of the vesting conditions set forth in Paragraph 2 above, any Restricted Stock Units that have not vested as of such date shall automatically and without notice terminate and be forfeited, and neither the Grantee nor any of his or her successors, heirs, assigns, or personal representatives will thereafter have any further rights or interests in such unvested Restricted Stock Units.

(a) Termination Due to Death. If the Grantee's Service Relationship with the Company or a Subsidiary terminates by reason of the Grantee's death, then any Restricted Stock Units that have not vested as of the Grantee's death shall immediately vest in full as of the date of death.

(b) Termination Due to Permanent Disability. If the Grantee's Service Relationship with the Company or a Subsidiary terminates by reason of the Grantee's permanent disability (as defined below), then any Restricted Stock Units under this Award that have not vested as of the last date of the Grantee's Service Relationship shall immediately vest in full as of such date. For purposes of this Award, "permanent disability" shall mean the inability of the

Grantee to continue in his or her position for the Company (or an Affiliate) by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as determined by the Company in its sole discretion.

4. Issuance of Shares of Stock. As soon as practicable following each Vesting Date (but in no event later than two and one-half months after the end of the year in which the Vesting Date occurs), the Company shall issue to the Grantee the number of shares of Stock equal to the aggregate number of Restricted Stock Units that have vested pursuant to Paragraph 2 of this Agreement on such date and the Grantee shall thereafter have all the rights of a stockholder of the Company with respect to such shares.

5. Incorporation of Plan. Notwithstanding anything herein to the contrary, this Agreement shall be subject to and governed by all the terms and conditions of the Plan, including the powers of the Administrator set forth in Section 2(b) of the Plan. Capitalized terms in this Agreement shall have the meaning specified in the Plan, unless a different meaning is specified herein.

6. Tax Withholding. In connection with the settlement of vested Restricted Stock Units, the Company shall issue the shares of Stock referred to in Paragraph 4 to a broker designated by the Company and acting on behalf and for the account of the Grantee with instructions to (i) sell a number of shares of such Stock sufficient to satisfy the applicable withholding taxes which arise in connection with such settlement; provided, that the amount sold does not exceed the maximum statutory tax rate or such lesser amount as is necessary to avoid liability accounting treatment, along with any applicable third-party commission, and (ii) remit the proceeds of such sale to the Company. In the event the sale proceeds are insufficient to fully satisfy the applicable withholding taxes, the Grantee authorizes withholding from payroll and any other amounts payable to the Grantee, in the same calendar year, and otherwise agrees to make adequate provision through the submission of cash, a check or its equivalent for any sums required to satisfy the applicable withholding taxes. It is the intent of the parties that this Paragraph 6 comply with the requirements of Rule 10b5-1(c)(1)(i)(B) under the Exchange Act, and the Agreement will be interpreted to comply with the requirements of Rule 10b5-1(c) under the Exchange Act. Unless the withholding tax obligations of the Company and/or any Affiliate thereof are satisfied, the Company shall have no obligation to issue any shares of Stock on the Grantee's behalf pursuant to the vesting of the Restricted Stock Units.

7. Section 409A of the Code. This Agreement shall be interpreted in such a manner that all provisions relating to the settlement of the Award are exempt from the requirements of Section 409A of the Code as "short-term deferrals" as described in Section 409A of the Code.

8. No Obligation to Continue Service Relationship. Neither the Company nor any Subsidiary is obligated by or as a result of the Plan or this Agreement to continue the Grantee's Service Relationship with the Company or a Subsidiary and neither the Plan nor this Agreement shall interfere in any way with the right of the Company or any Subsidiary to terminate the Grantee's Service Relationship with the Company or a Subsidiary at any time.

9. Integration. This Agreement constitutes the entire agreement between the parties with respect to this Award and supersedes all prior agreements and discussions between the parties concerning such subject matter.

10. Data Privacy Consent. In order to administer the Plan and this Agreement and to implement or structure future equity grants, the Company, its subsidiaries and affiliates and certain agents thereof (together, the "Relevant Companies") may process any and all personal or professional data, including but not limited to Social Security or other identification number, home address and telephone number, date of birth and other information that is necessary or

desirable for the administration of the Plan and/or this Agreement (the “Relevant Information”). By entering into this Agreement, the Grantee (i) authorizes the Company to collect, process, register and transfer to the Relevant Companies all Relevant Information; (ii) waives any privacy rights the Grantee may have with respect to the Relevant Information; (iii) authorizes the Relevant Companies to store and transmit such information in electronic form; and (iv) authorizes the transfer of the Relevant Information to any jurisdiction in which the Relevant Companies consider appropriate. The Grantee shall have access to, and the right to change, the Relevant Information. Relevant Information will only be used in accordance with applicable law.

11. Notices. Notices hereunder shall be mailed or delivered to the Company at its principal place of business and shall be mailed or delivered to the Grantee at the address on file with the Company or, in either case, at such other address as one party may subsequently furnish to the other party in writing.

Moderna, Inc.

By:

Name:
Title:

The foregoing Agreement is hereby accepted and the terms and conditions thereof hereby agreed to by the undersigned. Electronic acceptance of this Agreement pursuant to the Company’s instructions to the Grantee (including through an online acceptance process) is acceptable.

[Signed Electronically]
Acceptance Date: [Acceptance Date]

Appendix A: Vesting Schedule

[Vesting Schedule]

**NON-QUALIFIED STOCK OPTION AGREEMENT
FOR COMPANY EMPLOYEES
UNDER THE MODERNA, INC.
2018 STOCK OPTION AND INCENTIVE PLAN**

Name of Optionee: [Participant Name]

No. of Option Shares: [Number of Shares Granted]

Option Exercise Price per Share: \$[Grant Price]

Grant Date: [Grant date]

Expiration Date: [Expiration Date]

Pursuant to the Moderna, Inc. 2018 Stock Option and Incentive Plan as amended through the date hereof (the "Plan"), Moderna, Inc. (the "Company") hereby grants to the Optionee named above an option (the "Stock Option") to purchase on or prior to the Expiration Date specified above all or part of the number of shares of Common Stock, par value \$0.0001 per share (the "Stock") of the Company specified above at the Option Exercise Price per Share specified above subject to the terms and conditions set forth herein and in the Plan. This Stock Option is not intended to be an "incentive stock option" under Section 422 of the Internal Revenue Code of 1986, as amended.

1. Exercisability Schedule. No portion of this Stock Option may be exercised until such portion shall have become exercisable. Except as set forth below in Appendix A, and subject to the discretion of the Administrator (as defined in Section 2 of the Plan) to accelerate the exercisability schedule hereunder, this Stock Option shall be exercisable with respect to the following number of Option Shares on the dates indicated on Appendix A to this Agreement so long as the Optionee continues to have a Service Relationship with the Company or a Subsidiary on such dates.

Once exercisable, this Stock Option shall continue to be exercisable at any time or times prior to the close of business on the Expiration Date, subject to the provisions hereof and of the Plan.

2. Manner of Exercise.

(a) The Optionee may exercise this Stock Option only in the following manner: from time to time on or prior to the Expiration Date of this Stock Option, the Optionee may give written notice to the Administrator of his or her election to purchase some or all of the Option Shares purchasable at the time of such notice. This notice shall specify the number of Option Shares to be purchased.

Payment of the purchase price for the Option Shares may be made by one or more of the following methods: (i) in cash, by certified or bank check or other instrument acceptable to the Administrator; (ii) if permitted by the Administrator, through the delivery (or attestation to the ownership) of shares of Stock that have been purchased by the Optionee on the open market or that are beneficially owned by the Optionee and are not then subject to any restrictions under any Company plan and that otherwise satisfy any holding periods as may be required by the

Administrator; (iii) by the Optionee delivering to the Company a properly executed exercise notice together with irrevocable instructions to a broker to promptly deliver to the Company cash or a check payable and acceptable to the Company to pay the option purchase price, provided that in the event the Optionee chooses to pay the option purchase price as so provided, the Optionee and the broker shall comply with such procedures and enter into such agreements of indemnity and other agreements as the Administrator shall prescribe as a condition of such payment procedure; (iv) if permitted by the Administrator, by a "net exercise" arrangement pursuant to which the Company will reduce the number of shares of Stock issuable upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price; or (v) a combination of (i), (ii), (iii) and (iv) above. Payment instruments will be received subject to collection.

The transfer to the Optionee on the records of the Company or of the transfer agent of the Option Shares will be contingent upon (i) the Company's receipt from the Optionee of the full purchase price for the Option Shares, as set forth above, (ii) the fulfillment of any other requirements contained herein or in the Plan or in any other agreement or provision of laws, and (iii) the receipt by the Company of any agreement, statement or other evidence that the Company may require to satisfy itself that the issuance of Stock to be purchased pursuant to the exercise of Stock Options under the Plan and any subsequent resale of the shares of Stock will be in compliance with applicable laws and regulations. In the event the Optionee chooses to pay the purchase price by previously-owned shares of Stock through the attestation method, the number of shares of Stock transferred to the Optionee upon the exercise of the Stock Option shall be net of the Shares attested to.

(b) The shares of Stock purchased upon exercise of this Stock Option shall be transferred to the Optionee on the records of the Company or of the transfer agent upon compliance to the satisfaction of the Administrator with all requirements under applicable laws or regulations in connection with such transfer and with the requirements hereof and of the Plan. The determination of the Administrator as to such compliance shall be final and binding on the Optionee. The Optionee shall not be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Stock subject to this Stock Option unless and until this Stock Option shall have been exercised pursuant to the terms hereof, the Company or the transfer agent shall have transferred the shares to the Optionee, and the Optionee's name shall have been entered as the stockholder of record on the books of the Company. Thereupon, the Optionee shall have full voting, dividend and other ownership rights with respect to such shares of Stock.

(c) The minimum number of shares with respect to which this Stock Option may be exercised at any one time shall be 100 shares, unless the number of shares with respect to which this Stock Option is being exercised is the total number of shares subject to exercise under this Stock Option at the time.

(d) Notwithstanding any other provision hereof or of the Plan, no portion of this Stock Option shall be exercisable after the Expiration Date hereof.

3. Termination of Service Relationship. If the Optionee's Service Relationship with the Company or a Subsidiary (as defined in the Plan) is terminated, the period within which to exercise the Stock Option may be subject to earlier termination as set forth below.

(a) Termination Due to Death. If the Optionee's Service Relationship with the Company or a Subsidiary terminates by reason of the Optionee's death, then any portion of this Stock Option that has not vested as of the Optionee's death shall immediately vest in full as of the date of death. Following any termination due to death, this Stock Option may thereafter be exercised by the Optionee's legal representative or legatee for a period of 12 months from the date of death or until the Expiration Date, if earlier.

(b) Termination Due to Permanent Disability. If the Optionee's Service Relationship with the Company or a Subsidiary terminates by reason of the Optionee's permanent disability (as defined below), then any portion of this Stock Option that has not vested as of the last date of the Optionee's Service Relationship (the "Accelerated Vesting Date") shall immediately vest in full as of the Accelerated Vesting Date. Following any termination due to disability, this Stock Option may thereafter be exercised by the Optionee for a period of 12 months from the Accelerated Vesting Date or until the Expiration Date, if earlier. For purposes of this Stock Option, "permanent disability" shall mean the inability of the Optionee to continue in his or her position for the Company (or an Affiliate) by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as determined by the Company in its sole discretion.

(c) Termination for Cause. If the Optionee's Service Relationship with the Company or a Subsidiary terminates for Cause, any portion of this Stock Option outstanding on such date shall terminate immediately and be of no further force and effect. For purposes hereof, "Cause" shall mean, unless otherwise provided in an employment or other service agreement between the Company and the Optionee, a determination by the Administrator that the Optionee shall be dismissed as a result of (i) any material breach by the Optionee of any agreement between the Optionee and the Company; (ii) the conviction of, indictment for or plea of nolo contendere by the Optionee to a felony or a crime involving moral turpitude; or (iii) any material misconduct or willful and deliberate non-performance (other than by reason of disability) by the Optionee of the Optionee's duties to the Company.

(d) Other Termination. If the Optionee's Service Relationship with the Company or a Subsidiary terminates for any reason other than the Optionee's death, the Optionee's permanent disability or Cause, and unless otherwise determined by the Administrator, any portion of this Stock Option outstanding on such date may be exercised, to the extent exercisable on the date of termination, for a period of three months from the date of termination or until the Expiration Date, if earlier. Any portion of this Stock Option that is not exercisable on the date of termination shall terminate immediately and be of no further force or effect.

The Administrator's determination of the reason for termination of the Optionee's Service Relationship with the Company or a Subsidiary shall be conclusive and binding on the Optionee and his or her representatives or legatees.

4. Incorporation of Plan. Notwithstanding anything herein to the contrary, this Stock Option shall be subject to and governed by all the terms and conditions of the Plan, including the powers of the Administrator set forth in Section 2(b) of the Plan. Capitalized terms in this Agreement shall have the meaning specified in the Plan, unless a different meaning is specified herein.

5. Transferability. This Agreement is personal to the Optionee, is non-assignable and is not transferable in any manner, by operation of law or otherwise, other than by will or the laws of descent and distribution. This Stock Option is exercisable, during the Optionee's lifetime, only by the Optionee, and thereafter, only by the Optionee's legal representative or legatee.

6. Tax Withholding. The Optionee shall, not later than the date as of which the exercise of this Stock Option becomes a taxable event for Federal income tax purposes, pay to the Company or make arrangements satisfactory to the Administrator for payment of any Federal, state, and local taxes required by law to be withheld on account of such taxable event. The Company shall have the authority to cause the minimum required tax withholding obligation to be satisfied, in whole or in part, by withholding from shares of Stock to be issued to the

Optionee a number of shares of Stock with an aggregate Fair Market Value that would satisfy the minimum withholding amount due.

7. No Obligation to Continue Service Relationship. Neither the Company nor any Subsidiary is obligated by or as a result of the Plan or this Agreement to continue the Optionee in a Service Relationship with the Company or a Subsidiary and neither the Plan nor this Agreement shall interfere in any way with the right of the Company or any Subsidiary to terminate the Optionee's Service Relationship with the Company or a Subsidiary at any time.

8. Integration. This Agreement constitutes the entire agreement between the parties with respect to this Stock Option and supersedes all prior agreements and discussions between the parties concerning such subject matter.

9. Data Privacy Consent. In order to administer the Plan and this Agreement and to implement or structure future equity grants, the Company, its subsidiaries and affiliates and certain agents thereof (together, the "Relevant Companies") may process any and all personal or professional data, including but not limited to Social Security or other identification number, home address and telephone number, date of birth and other information that is necessary or desirable for the administration of the Plan and/or this Agreement (the "Relevant Information"). By entering into this Agreement, the Optionee (i) authorizes the Company to collect, process, register and transfer to the Relevant Companies all Relevant Information; (ii) waives any privacy rights the Optionee may have with respect to the Relevant Information; (iii) authorizes the Relevant Companies to store and transmit such information in electronic form; and (iv) authorizes the transfer of the Relevant Information to any jurisdiction in which the Relevant Companies consider appropriate. The Optionee shall have access to, and the right to change, the Relevant Information. Relevant Information will only be used in accordance with applicable law.

10. Notices. Notices hereunder shall be mailed or delivered to the Company at its principal place of business and shall be mailed or delivered to the Optionee at the address on file with the Company or, in either case, at such other address as one party may subsequently furnish to the other party in writing.

Moderna, Inc.

By:

Name:

Title:

The foregoing Agreement is hereby accepted and the terms and conditions thereof hereby agreed to by the undersigned. Electronic acceptance of this Agreement pursuant to the Company's instructions to the Optionee (including through an online acceptance process) is acceptable.

Acceptance Date: [Acceptance Date]

Appendix A: Vesting Schedule

[Vesting Schedule]

**RESTRICTED STOCK UNIT AWARD AGREEMENT
FOR NON-EMPLOYEE DIRECTORS
UNDER THE MODERNA, INC.
2018 STOCK OPTION AND INCENTIVE PLAN**

Name of Grantee: **[Participant Name]**

No. of Restricted Stock Units: **[Number of Shares Granted]**

Grant Date: **[Grant date]**

Pursuant to the Moderna, Inc. 2018 Stock Option and Incentive Plan as amended through the date hereof (the "Plan"), Moderna, Inc. (the "Company") hereby grants an award of the number of Restricted Stock Units listed above (an "Award") to the Grantee named above. Each Restricted Stock Unit shall relate to one share of Common Stock, par value \$0.0001 per share (the "Stock") of the Company.

1. Restrictions on Transfer of Award. This Award may not be sold, transferred, pledged, assigned or otherwise encumbered or disposed of by the Grantee, and any shares of Stock issuable with respect to the Award may not be sold, transferred, pledged, assigned or otherwise encumbered or disposed of until (i) the Restricted Stock Units have vested as provided in Paragraph 2 of this Agreement and (ii) shares of Stock have been issued to the Grantee in accordance with the terms of the Plan and this Agreement.

2. Vesting of Restricted Stock Units. The restrictions and conditions of Paragraph 1 of this Agreement shall lapse on the Vesting Date or Dates specified in the following schedule so long as the Grantee remains in service as a member of the Board on such Dates. If a series of Vesting Dates is specified, then the restrictions and conditions in Paragraph 1 shall lapse only with respect to the number of Restricted Stock Units specified as vested on such date.

Notwithstanding the foregoing, in the event of a Sale Event, 100% of the then-outstanding and unvested Restricted Stock Units shall immediately be deemed vested on the date of such Sale Event; provided, that the Grantee remains in service as a member of the Board until the date of such Sale Event. The Administrator may at any time accelerate the vesting schedule specified in Appendix A.

3. Termination of Service. If the Grantee's service as a member of the Board terminates for any reason (other than death or permanent disability) prior to the satisfaction of the vesting conditions set forth in Paragraph 2 above, any Restricted Stock Units that have not vested as of such date shall automatically and without notice terminate and be forfeited, and neither the Grantee nor any of his or her successors, heirs, assigns, or personal representatives will thereafter have any further rights or interests in such unvested Restricted Stock Units.

(a) Termination Due to Death. If the Grantee's Service Relationship with the Company or a Subsidiary terminates by reason of the Grantee's death, then any Restricted Stock Units that have not vested as of the Grantee's death shall immediately vest in full as of the date of death.

(b) Termination Due to Permanent Disability. If the Grantee's service as a member of the Board terminates by reason of the Grantee's permanent disability (as defined below), then any Restricted Stock Units under this Award that have not vested as of the last date of the Grantee's service as a member of the Board of Directors shall immediately vest in full as

of such date. For purposes of this Award, “permanent disability” shall mean the inability of the Optionee to continue to perform service as a member of the Board of Directors by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as determined by the Company in its sole discretion.

4. Issuance of Shares of Stock. As soon as practicable following each Vesting Date (but in no event later than two and one-half months after the end of the year in which the Vesting Date occurs), the Company shall issue to the Grantee the number of shares of Stock equal to the aggregate number of Restricted Stock Units that have vested pursuant to Paragraph 2 of this Agreement on such date and the Grantee shall thereafter have all the rights of a stockholder of the Company with respect to such shares.

5. Incorporation of Plan. Notwithstanding anything herein to the contrary, this Agreement shall be subject to and governed by all the terms and conditions of the Plan, including the powers of the Administrator set forth in Section 2(b) of the Plan. Capitalized terms in this Agreement shall have the meaning specified in the Plan, unless a different meaning is specified herein.

6. Section 409A of the Code. This Agreement shall be interpreted in such a manner that all provisions relating to the settlement of the Award are exempt from the requirements of Section 409A of the Code as “short-term deferrals” as described in Section 409A of the Code.

7. No Obligation to Continue as a Director. Neither the Plan nor this Award confers upon the Grantee any rights with respect to continuance as a Director.

8. Integration. This Agreement constitutes the entire agreement between the parties with respect to this Award and supersedes all prior agreements and discussions between the parties concerning such subject matter.

9. Data Privacy Consent. In order to administer the Plan and this Agreement and to implement or structure future equity grants, the Company, its subsidiaries and affiliates and certain agents thereof (together, the “Relevant Companies”) may process any and all personal or professional data, including but not limited to Social Security or other identification number, home address and telephone number, date of birth and other information that is necessary or desirable for the administration of the Plan and/or this Agreement (the “Relevant Information”). By entering into this Agreement, the Grantee (i) authorizes the Company to collect, process, register and transfer to the Relevant Companies all Relevant Information; (ii) waives any privacy rights the Grantee may have with respect to the Relevant Information; (iii) authorizes the Relevant Companies to store and transmit such information in electronic form; and (iv) authorizes the transfer of the Relevant Information to any jurisdiction in which the Relevant Companies consider appropriate. The Grantee shall have access to, and the right to change, the Relevant Information. Relevant Information will only be used in accordance with applicable law.

10. Notices. Notices hereunder shall be mailed or delivered to the Company at its principal place of business and shall be mailed or delivered to the Grantee at the address on file with the Company or, in either case, at such other address as one party may subsequently furnish to the other party in writing.

Moderna, Inc.

By:

Name:
Title:

The foregoing Agreement is hereby accepted and the terms and conditions thereof hereby agreed to by the undersigned. Electronic acceptance of this Agreement pursuant to the Company's instructions to the Grantee (including through an online acceptance process) is acceptable.

Acceptance Date: **[Acceptance Date]**

Appendix A: Vesting Schedule

[Vesting Schedule]

**NON-QUALIFIED STOCK OPTION AGREEMENT
FOR NON-EMPLOYEE DIRECTORS
UNDER THE MODERNA, INC.
2018 STOCK OPTION AND INCENTIVE PLAN**

Name of Optionee: [Participant Name]

No. of Option Shares: [Number of Shares Granted]

Option Exercise Price per Share: [Grant Price]

Grant Date: [Grant date]

Expiration Date: [Expiration Date]

Pursuant to the Moderna, Inc. 2018 Stock Option and Incentive Plan as amended through the date hereof (the "Plan"), Moderna, Inc. (the "Company") hereby grants to the Optionee named above, who is a Director of the Company but is not an employee of the Company, an option (the "Stock Option") to purchase on or prior to the Expiration Date specified above all or part of the number of shares of Common Stock, par value \$0.0001 per share (the "Stock"), of the Company specified above at the Option Exercise Price per Share specified above subject to the terms and conditions set forth herein and in the Plan. This Stock Option is not intended to be an "incentive stock option" under Section 422 of the Internal Revenue Code of 1986, as amended.

1. Exercisability Schedule. No portion of this Stock Option may be exercised until such portion shall have become exercisable. Except as set forth below, and subject to the discretion of the Administrator (as defined in Section 2 of the Plan) to accelerate the exercisability schedule hereunder, this Stock Option shall be exercisable with respect to the following number of Option Shares on the dates indicated so long as the Optionee remains in service as a member of the Board on such dates:

[Vesting Date and Quantity]

Notwithstanding the foregoing, in the event of a Sale Event, 100% of the then-outstanding and unvested Option Shares shall immediately be deemed vested and exercisable on the date of such Sale Event; provided, that the Optionee remains in service as a member of the Board until the date of such Sale Event. Once exercisable, this Stock Option shall continue to be exercisable at any time or times prior to the close of business on the Expiration Date, subject to the provisions hereof and of the Plan.

2. Manner of Exercise.

(a) The Optionee may exercise this Stock Option only in the following manner: from time to time on or prior to the Expiration Date of this Stock Option, the Optionee may give written notice to the Administrator of his or her election to purchase some or all of the Option Shares purchasable at the time of such notice. This notice shall specify the number of Option Shares to be purchased.

Payment of the purchase price for the Option Shares may be made by one or more of the following methods: (i) in cash, by certified or bank check or other instrument acceptable to the Administrator; (ii) if permitted by the Administrator, through the delivery (or attestation to the

ownership) of shares of Stock that have been purchased by the Optionee on the open market or that are beneficially owned by the Optionee and are not then subject to any restrictions under any Company plan and that otherwise satisfy any holding periods as may be required by the Administrator; (iii) by the Optionee delivering to the Company a properly executed exercise notice together with irrevocable instructions to a broker to promptly deliver to the Company cash or a check payable and acceptable to the Company to pay the option purchase price, provided that in the event the Optionee chooses to pay the option purchase price as so provided, the Optionee and the broker shall comply with such procedures and enter into such agreements of indemnity and other agreements as the Administrator shall prescribe as a condition of such payment procedure; (iv) if permitted by the Administrator, by a "net exercise" arrangement pursuant to which the Company will reduce the number of shares of Stock issuable upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price; or (v) a combination of (i), (ii), (iii) and (iv) above. Payment instruments will be received subject to collection.

The transfer to the Optionee on the records of the Company or of the transfer agent of the Option Shares will be contingent upon (i) the Company's receipt from the Optionee of the full purchase price for the Option Shares, as set forth above, (ii) the fulfillment of any other requirements contained herein or in the Plan or in any other agreement or provision of laws, and (iii) the receipt by the Company of any agreement, statement or other evidence that the Company may require to satisfy itself that the issuance of Stock to be purchased pursuant to the exercise of Stock Options under the Plan and any subsequent resale of the shares of Stock will be in compliance with applicable laws and regulations. In the event the Optionee chooses to pay the purchase price by previously-owned shares of Stock through the attestation method, the number of shares of Stock transferred to the Optionee upon the exercise of the Stock Option shall be net of the Shares attested to.

(b) The shares of Stock purchased upon exercise of this Stock Option shall be transferred to the Optionee on the records of the Company or of the transfer agent upon compliance to the satisfaction of the Administrator with all requirements under applicable laws or regulations in connection with such transfer and with the requirements hereof and of the Plan. The determination of the Administrator as to such compliance shall be final and binding on the Optionee. The Optionee shall not be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Stock subject to this Stock Option unless and until this Stock Option shall have been exercised pursuant to the terms hereof, the Company or the transfer agent shall have transferred the shares to the Optionee, and the Optionee's name shall have been entered as the stockholder of record on the books of the Company. Thereupon, the Optionee shall have full voting, dividend and other ownership rights with respect to such shares of Stock.

(c) The minimum number of shares with respect to which this Stock Option may be exercised at any one time shall be 100 shares, unless the number of shares with respect to which this Stock Option is being exercised is the total number of shares subject to exercise under this Stock Option at the time.

(d) Notwithstanding any other provision hereof or of the Plan, no portion of this Stock Option shall be exercisable after the Expiration Date hereof.

3. Termination as Director. If the Optionee's service as a member of the Board ceases, the period within which to exercise the Stock Option may be subject to earlier termination as set forth below.

(a) Termination Due to Death or Permanent Disability. If the Optionee's service as a member of the Board terminates by reason of the Optionee's death or permanent disability, then any portion of this Stock Option that has not vested as of the date of such death or

permanent disability shall immediately vest in full as of the date of death or the last day of the Optionee's service as a member of the Board of Directors, as applicable (the "Accelerated Vesting Date"). Following any termination due to death or permanent disability, this Stock Option may thereafter be exercised by the Optionee or the Optionee's legal representative or legatee for a period of 12 months from the Accelerated Vesting Date or until the Expiration Date, if earlier. For purposes of this Stock Option, "permanent disability" shall mean the inability of the Optionee to continue to perform service as a member of the Board of Directors by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as determined by the Company in its sole discretion.

(b) Other Termination. If the Optionee's service as a member of the Board ceases for any reason other than the Optionee's death or permanent disability, any portion of this Stock Option outstanding on such date may be exercised, to the extent exercisable on the date the Optionee ceased to be a Director, for a period of six months from the date the Optionee ceased to be a Director or until the Expiration Date, if earlier. Any portion of this Stock Option that is not exercisable on the date the Optionee ceases to be a Director shall terminate immediately and be of no further force or effect.

4. Incorporation of Plan. Notwithstanding anything herein to the contrary, this Stock Option shall be subject to and governed by all the terms and conditions of the Plan, including the powers of the Administrator set forth in Section 2(b) of the Plan. Capitalized terms in this Agreement shall have the meaning specified in the Plan, unless a different meaning is specified herein.

5. Transferability. This Agreement is personal to the Optionee, is non-assignable and is not transferable in any manner, by operation of law or otherwise, other than by will or the laws of descent and distribution. This Stock Option is exercisable, during the Optionee's lifetime, only by the Optionee, and thereafter, only by the Optionee's legal representative or legatee.

6. No Obligation to Continue as a Director. Neither the Plan nor this Stock Option confers upon the Optionee any rights with respect to continuance as a Director.

7. Integration. This Agreement constitutes the entire agreement between the parties with respect to this Stock Option and supersedes all prior agreements and discussions between the parties concerning such subject matter.

8. Data Privacy Consent. In order to administer the Plan and this Agreement and to implement or structure future equity grants, the Company, its subsidiaries and affiliates and certain agents thereof (together, the "Relevant Companies") may process any and all personal or professional data, including but not limited to Social Security or other identification number, home address and telephone number, date of birth and other information that is necessary or desirable for the administration of the Plan and/or this Agreement (the "Relevant Information"). By entering into this Agreement, the Optionee (i) authorizes the Company to collect, process, register and transfer to the Relevant Companies all Relevant Information; (ii) waives any privacy rights the Optionee may have with respect to the Relevant Information; (iii) authorizes the Relevant Companies to store and transmit such information in electronic form; and (iv) authorizes the transfer of the Relevant Information to any jurisdiction in which the Relevant Companies consider appropriate. The Optionee shall have access to, and the right to change, the Relevant Information. Relevant Information will only be used in accordance with applicable law.

9. Notices. Notices hereunder shall be mailed or delivered to the Company at its principal place of business and shall be mailed or delivered to the Optionee at the address on file with the Company or, in either case, at such other address as one party may subsequently furnish to the other party in writing.

Moderna, Inc.

By:

Name:

Title:

The foregoing Agreement is hereby accepted and the terms and conditions thereof hereby agreed to by the undersigned. Electronic acceptance of this Agreement pursuant to the Company's instructions to the Optionee (including through an online acceptance process) is acceptable.

Acceptance Date: [\[Acceptance Date\]](#)

Certain confidential portions of this exhibit have been omitted and replaced with "[***]". Such identified information has been excluded from this exhibit because it (i) is not material and (ii) is the type of information that the registrant treats as private or confidential.

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE OF PAGES

1 3

2. AMENDMENT/MODIFICATION NO.
P00011

3. EFFECTIVE DATE
See Block 16C

4. REQUISITION/PURCHASE REQ. NO.
See Schedule

5. PROJECT NO.(If applicable)

6. ISSUED BY CODE

ASPR-BARDA

7. ADMINISTERED BY (If other than item 6) CODE

ASPR-BARDA02

ASPR-BARDA
200 Independence Ave., S.W. Room 640-G
Washington DC 20201

US DEPT OF HEALTH & HUMAN SERVICES
ASST SEC OF PREPAREDNESS & RESPONSE ACQ MANAGEMENT, CONTRACTS, &
GRANTS O'NEILL HOUSE OFFICE BUILDING
Washington DC 20515

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)

9A. AMENDMENT OF SOLICITATION NO.

MODERNATX, INC 1492235
Attn: [***]
MODERNATX, INC. 200 TECHNOLOGY
200 TECHNOLOGY SQ
CAMBRIDGE MA 021393578

9B. DATED (SEE ITEM 11)

X

10A. MOD. OF CONTRACT/ORDER NO.
75A50120C00034

X

10B. DATED (SEE ITEM 13)

CODE 8PTM0

FACILITY CODE

04/03/2020

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods:

(a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

See Schedule

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS.
IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

- A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
- B. THE ABOVE NUMBERED CONTRACT /ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).
- C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
- X D. OTHER (Specify type of modification and authority)
FAR 43.103(a)

E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.

14. DESCRIPTION OF AMENDMENT /MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)

Tax ID Number: 27-0226313

DUNS Number: 069723520

The purpose of this "no cost" bilateral modification is to:

- Incorporate Executive Order 14042 - FAR Deviation Clause 52.223-99, Ensuring Adequate COVID Safety Protocols for Federal Contractors into Section I of the contract.

- Update Section G.8 Negotiated Indirect Rates and Ceiling

1. The following is hereby incorporated by full text, at no additional cost to the Government, into Section I:

Continued ...

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)
Shaun Ryan, SVP & Deputy General Counsel

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)
[***]

15B. CONTRACT OR/OFFEROR

15C. DATE SIGNED

16B. UNITED STATES OF AMERICA

16C. DATE SIGNED

/s/ Shaun Ryan

1/20/2022

BY [***]

2021.1.05

(Signature of person authorized to sign)

(Signature of Contracting Officer)

Previous edition unusable

STANDARD FORM 30 (Rev. 10-83)
Prescribed by GSA
FAR (48 CFR) 53.243

CONTINUATION SHEET

REFERENCE NO. OF DOCUMENT BEING CONTINUED

PAGE OF
2 3NAME OF OFFEROR OR CONTRACTOR
MODERNATX, INC 1492235

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
	52.223-99 Ensuring Adequate COVID-19 Safety Protocols for Federal Contractors. ENSURING ADEQUATE COVID-19 SAFETY PROTOCOLS FOR FEDERAL CONTRACTORS(OCT 2021) (DEVIATION)				
	(a) Definition. As used in this clause - United States or its outlying areas means				
	(1) The fifty States;				
	(2) The District of Columbia;				
	(3) The commonwealths of Puerto Rico and the Northern Mariana Islands;				
	(4) The territories of American Samoa, Guam, and the and United States Virgin Islands; and				
	(5) The minor outlying islands of Baker Island, Howland Island, Jarvis Island, Johnston Atoll, Kingman Reef, Midway Islands, Navassa Island, Palmyra Atoll, and Wake Atoll.				
	(b) Authority. This clause implements Executive Order 14042, Ensuring Adequate COVID Safety Protocols for Federal Contractors, dated September 9, 2021 (published in the Federal Register on September 14, 2021, 86 FR 50985).				
	(c) Compliance. The Contractor shall comply with all guidance, including guidance conveyed through Frequently Asked Questions, as amended during the performance of this contract, for contractor or subcontractor workplace locations published by the Safer Federal Workforce Task Force (Task Force Guidance) at https://www.saferfederalworkforce.gov/contractors/ .				
	(d) Subcontracts. The Contractor shall include the substance of this clause, including this paragraph (d), in subcontracts at any tier that exceed the simplified acquisition threshold, as defined in Federal Acquisition Regulation 2.101 on the date of subcontract award, and are for services, including construction, performed in whole or in part within the United States or its outlying areas.				
	(End of clause)				
	2. The total amount, scope, period of performance and all other terms and conditions of the contract remain unchanged.				
	3. By signing this modification, MODERNATX, INC, hereby releases the Government from any and all liability under this contract for further equitable adjustments attributable to such fact or circumstance giving rise to this modification. Period of Performance: 04/03/2020 to 08/31/2023				

NSN 7540-01-152-8067

OPTIONAL FORM 336 (4-86) Sponsored by
GSA
FAR (48 CFR) 53.110

CONTINUATION PAGE**Section G.8 – Negotiated Indirect Rates and Ceiling**

Below are the FY21 Provisional Indirect Rates that will be added to the contract with this modification.

<u>Approved FY21 Provisional Rates</u>		
<u>Indirect Cost</u>	<u>%</u>	<u>Allocation Base</u>
Fringe	[***]%	Total Labor Dollars
TechDev Overhead	[***]%	TechDev Department Direct Labor Dollars + Fringe
Research Overhead	[***]%	Research Department Direct Labor Dollars + Fringe
DevOps Overhead	[***]%	DevOps Department Direct Labor Dollars + Fringe
G&A Overhead		
G&A	[***]%	Total Cost Input

The total amount, scope, period of performance and all other terms and conditions of the contract remain unchanged

Certain confidential portions of this exhibit have been omitted and replaced with "[***]". Such identified information has been excluded from this exhibit because it (i) is not material and (ii) is the type of information that the registrant treats as private or confidential.

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE OF PAGES

1 12

2. AMENDMENT/MODIFICATION NO.

3. EFFECTIVE DATE

4. REQUISITION/PURCHASE REQ. NO.

5. PROJECT NO.(If applicable)

P00018

5-Nov-2021

See Schedule

6. ISSUED BY CODE

W58P05

7. ADMINISTERED BY (If other than item 6) CODE

S2206A

ACC-APG - COVID RESPONSE - W58P05
6472 INTEGRITY COURT (BUILDING 4401)
ABERDEEN PROVING GROUND MD 21005-3013

DCMA BOSTON
495 SUMMER STREET
BOSTON MA 02210-2138

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)

9A. AMENDMENT OF SOLICITATION NO.

9B. DATED (SEE ITEM 11)

MODERNA US, INC.

[***]

200 TECHNOLOGY SQ
CAMBRIDGE MA 02139-3578

X

10A. MOD. OF CONTRACT/ORDER NO.
W911QY20C0100

X

10B. DATED (SEE ITEM 13)

CODE 8PTM0

FACILITY CODE

09-Aug-2020

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods:

(a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS.
IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

- A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
- B. THE ABOVE NUMBERED CONTRACT /ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).
- C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
- D. OTHER (Specify type of modification and authority)

X

E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.

14. DESCRIPTION OF AMENDMENT /MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)

Modification Control Number: [***]

See Block 14 Continuation Page

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)

Shaun Ryan, SVP & Deputy General Counsel

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)

[***]

TEL: [***] EMAIL: [***]

15B. CONTRACT OR/OFFEROR

/s/ Shaun Ryan

(Signature of person authorized to sign)

15C. DATE SIGNED

11/4/2021

16B. UNITED STATES OF AMERICA

BY [***]

(Signature of Contracting Officer)

16C. DATE SIGNED

5-Nov-2021

EXCEPTION TO SF 30
APPROVED BY OIRM 11-84

30-105-04

STANDARD FORM 30 (Rev. 10-83)
Prescribed by GSA
FAR (48 CFR) 53.243

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION SF 30 - BLOCK 14 CONTINUATION PAGE

The following have been added by full text: P00018

OBLIGATION AMOUNT: \$0.00

- a. The purpose of this modification (P00018) is to:
 - Update H.19 to reflect revised term agreed on by USG and Moderna (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties)
- b. This modification was requested by the program office to meet the Government's mission requirements.
- c. The total contract value and total funded amount remain unchanged.

SECTION H - SPECIAL CONTRACT REQUIREMENTS

The following have been modified:

H.1 Key Personnel

Any key personnel specified in this contract are considered to be essential to work performance. At least thirty (30) calendar days prior to the Contractor voluntarily diverting any of the specified individuals to other programs or contracts the Contractor shall notify the Contracting Officer and shall submit a justification for the diversion or replacement and a request to replace the individual. The request must identify the proposed replacement and provide an explanation of how the replacement's skills, experience, and credentials meet or exceed the requirements of the contract (including, when applicable, Human Subjects Testing requirements). If the employee of the Contractor is terminated for cause or separates from the Contractor voluntarily with less than thirty (30) calendar-day notice, the Contractor shall provide the maximum notice practicable under the circumstances. The Contractor shall not divert, replace, or announce any such change to key personnel without the written consent of the Contracting Officer. The contract will be modified to add or delete key personnel as necessary to reflect the agreement of the parties. The following individuals are determined to be key personnel:

Name	Title
***	***
***	***
***	***
***	***
***	***
***	***
***	***
***	***

H.2 Substitution of Key Personnel

The Contractor agrees to assign to the contract those persons whose resumes/CVs were submitted with the proposal who are necessary to fill the requirements of the contract. No substitutions shall be made except in accordance with this clause.

All requests for substitution must provide a detailed explanation of the circumstance necessitating the proposed substitution, a complete resume for the proposed substitute and any other information requested by the contracting officer to approve or disapprove the proposed substitution. All proposed substitutes must have qualifications that are equal to or higher than the qualifications of the person to be replaced. The contracting officer or authorized representative will evaluate such requests and promptly notify the contractor of his approval or disapproval thereof.

H.3 Disclosure of Information:

Performance under this contract may require the Contractor to access non-public data and information proprietary to a Government agency, another Government Contractor or of such nature that its dissemination or use other than as specified in the work statement would be adverse to the interests of the Government or others. Neither the Contractor, nor Contractor personnel, shall divulge nor release data nor information developed or obtained under performance of this contract, except authorized by Government personnel or upon written approval of the CO which the KO will provide in accordance with OWS or other Government policies and/or guidance. The Contractor shall not use, disclose, or reproduce proprietary data that bears a restrictive legend, other than as specified in this contract, or any information at all regarding this agency.

The Contractor shall comply with all applicable Government requirements for protection of non-public information. Unauthorized disclosure of nonpublic information is prohibited by the Government's rules. Unauthorized disclosure may result in termination of the contract, replacement of a Contractor employee, or other appropriate redress. Neither the Contractor nor the Contractor's employees shall disclose or cause to be disseminated, any information concerning the operations of the activity, which could result in, or increase the likelihood of, the possibility of a breach of the activity's security or interrupt the continuity of its operations.

No information related to data obtained under this contract shall be released or publicized without the prior written consent of the COR, whose approval shall not be unreasonably withheld, conditioned, or delayed, provided that no such consent is required to comply with any law, rule, regulation, court ruling or similar order; for submission to any government entity' for submission to any securities exchange on which the Contractor's (or its parent corporation's) securities may be listed for trading; or to third parties relating to securing, seeking, establishing or maintaining regulatory or other legal approvals or compliance, financing and capital raising activities, or mergers, acquisitions, or other business transactions. The exceptions identified in this paragraph apply to all disclosures under this Section H.3 except to the extent that a disclosure is otherwise prohibited by law.

H.4 Publication and Publicity

The contractor shall not release any reports, manuscripts, press releases, or abstracts about the work being performed under this contract without written notice in advance to the Government.

- a. Unless otherwise specified in this contract, the contractor may publish the results of its work under this contract. The contractor shall promptly send a copy of each submission to the COR for security review prior to submission. The contractor shall also inform the COR when the abstract article or other publication is published, and furnish a copy of it as finally published.
 - b. Unless authorized in writing by the CO, the contractor shall not display the DoD logo including Operating Division or Staff Division logos on any publications.
 - c. The contractor shall not reference the products(s) or services(s) awarded under this contract in commercial advertising, as defined in FAR 31.205-1, in any manner which states or implies DoD approval or endorsement of the product(s) or service(s) provided.
 - d. The contractor shall include this clause, including this section (d) in all subcontracts where the subcontractor may propose publishing the results of its work under the subcontract. The contractor shall acknowledge the support of the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority whenever publicizing the work under this contract in any media by including an acknowledgement substantially as follows:
-

“This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract Number W911QY-20-C-0100.”

H.5 Confidentiality of Information

- a. Confidential information, as used in this article, means non-public information or data of a personal nature about an individual, or proprietary information or data submitted by or pertaining to an institution or organization.
- b. The Contracting Officer and the Contractor may, by mutual consent, identify elsewhere in this contract specific information and/or categories of information which the Government will furnish to the Contractor or that the Contractor is expected to generate which is confidential. Similarly, the Contracting Officer and the Contractor may, by mutual consent, identify such confidential information from time to time during the performance of the contract. Failure to agree will be settled pursuant to the “Disputes” clause.
- c. If it is established elsewhere in this contract that information to be utilized under this contract, or a portion thereof, is subject to the Privacy Act, the Contractor will follow the rules and procedures of disclosure set forth in the Privacy Act of 1974, 5 U.S.C. 552a, and implementing regulations and policies, with respect to systems of records determined to be subject to the Privacy Act.
- d. Confidential information, as defined in paragraph (a) of this article, shall not be disclosed without the prior written consent of the individual, institution, or organization.
- e. Whenever the Contractor is uncertain with regard to the proper handling of material under the contract, or if the material in question is subject to the Privacy Act or is confidential information subject to the provisions of this article, the Contractor shall obtain a written determination from the Contracting Officer prior to any release, disclosure, dissemination, or publication.
- f. Contracting Officer Determinations will reflect the result of internal coordination with appropriate program and legal officials.
- g. The provisions of paragraph (d) of this article shall not apply to conflicting or overlapping provisions in other Federal, State or local laws.

ALL REQUIREMENTS OF THIS SECTION H.5 MUST BE PASSED TO ALL SUB-CONTRACTOR.

H.6 Regulatory Rights

This contract involves supply of a product that requires FDA pre-market approval or clearance before commercial authorization. Contractor is seeking FDA authorization or clearance for the commercialization of mRNA-1273, Moderna vaccine for SARS-CoV-2 Coronavirus (the “Technology”). The Contractor is the Sponsor of the Regulatory Application (an investigational new drug application (IND), investigational device exemption (IDE), emergency use authorization (EUA), new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), or 510(k) pre-market notification filing (510(k)) or another regulatory filing submitted to FDA) for the technology. As the Sponsor of the Regulatory Application to FDA (as the terms “sponsor” and “applicant” are defined or used in at 21 CFR §§3.2(c), 312.5, 600.3(t), 812.2(b), 812 Subpart C, or 814.20), the Contractor has certain standing before the FDA that entitles it to exclusive communications related to the Regulatory Application.

Accordingly, the Contractor and the Government agree to the following:

- a. DoD Medical Product Priority. PL 115-92 allows the DoD to request, and FDA to provide, assistance to expedite development of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing American military personnel. The contractor recognizes that only the DoD can utilize PL 115-92. As such, the contractor will work proactively with the Government to leverage this law to its maximum potential under this contract. The contractor shall submit Public Law 115-92 Sponsor Authorization Letter that will be delivered to the designated OWS POC(s) within [***] of award.
- b. [***].

H.7 Performance Based Payment Liquidated under Termination

Performance Based Payments (PBPs) have been authorized as a method of financing under this contract. In the event the Moderna's mRNA-1273 COVID Vaccine is unsuccessful in its bid to obtain EUA or FDA approval, the Government may issue a Termination for Convenience (T4C) in whole or in part, on this contract. Upon notice of a T4C, the contractor shall submit a termination settlement proposal, IAW FAR 52.249-2, Termination for Convenience of the Government (Fixed-Price).

H.8 Public Readiness and Emergency Preparedness (PREP) Act:

In accordance with the Public Readiness and Emergency Preparedness Act ("PREP Act"), Pub. L. No. 109-148, Division C, Section 2, as amended (codified at 42 U.S.C. § 247d-6d and 42 U.S.C. § 247d-6e), as well as the Secretary of HHS's Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 15198 (Mar. 17, 2020, effective Feb. 4, 2020), and amended on April 15, 2020, 85 Fed. Reg. 21012 (together, the "Prep Act Declaration"):

- (i) This Agreement is being entered into for purposes of facilitating the manufacture, testing, development, distribution, administration, and use of "Covered Countermeasures" for responding to the COVID-19 public health emergency, in accordance with Section VI of the PREP Act Declaration;
- (ii) Contractor's performance of this Agreement falls within the scope of the "Recommended Activities" for responding to the COVID-19 public health emergency, to the extent it is in accordance with Section III of the PREP Act Declaration; and
- (iii) Contractor is a "Covered Person" to the extent it is a person defined in Section V of the PREP Act

Declaration.

Therefore, in accordance with Sections IV and VII of the PREP Act Declaration as well as the PREP Act (42 U.S.C. § 247d-6d), the Department of Defense contracting via assisted acquisition on behalf of the HHS, expressly acknowledges and agrees that the HHS Declaration cited above, specifically its language providing immunity from suit and liability is applicable to this acquisition as long as Contractors activities fall within the terms and conditions of the PREP Act and the PREP Act Declaration.

The Government may not use, or authorize the use of, any products or materials provided under this contract, unless such use occurs in the United States (or a U.S. territory where U.S. law applies such as embassies, military and NATO installations) and is protected from liability under a declaration issued under the PREP Act, or a successor COVID-19 PREP Act Declaration of equal or greater scope. Any use where the application of the PREP Act is in question will be discussed with Moderna prior to use and, if the parties disagree on such use, the dispute will be resolved according to the "Disputes Clause" (52.233-1)

The items and technology covered by this Contract are being developed for both civil and military applications.

H.9 [***].

H.10 Ensuring Sufficient Supply of the Product

1. In recognition of the Government's significant funding for the development and manufacturing of the product in this contract and the Government's need to provide sufficient quantities of a COVID-19 vaccine to protect the United States population, the Government shall have the remedy described in this section to ensure sufficient supply of the product to meet the needs of the public health or national security. This remedy is not available to the Government unless and until both of the following conditions ((a) and (b)) are met:

a. Moderna gives written notice, required to be submitted to the Government [***], of:

(i) any formal management decision to terminate manufacturing of this product vaccine prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons or;

(ii) any formal management decision to discontinue sale of this product vaccine to the Government prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons; or

(iii) any filing that anticipates Federal bankruptcy protection; and

b. Moderna has submitted an Emergency Use Authorization application under §564 of the FD&C Act or a biologics license application provisions of §351(a) of the Public Health Service Act (PHSA).

2. If both conditions listed in section 1 occur, Moderna, upon the request of the Government, shall provide the following items necessary for the Government to pursue manufacturing of this product vaccine with a third party for exclusive sale to the U.S. Government:

a. a writing evidencing a non-exclusive, nontransferable, irrevocable (except for cause), royalty-free paid-up license to practice or have practiced for or on behalf of the U.S. Government any Moderna Background Patent, Copyright, other Moderna Intellectual Property, Moderna Know-How, Moderna Technical Data rights necessary to manufacture doses of the mRNA-1273 vaccine;

b. necessary FDA regulatory filings or authorizations owned or controlled by Moderna related to this product vaccine and any confirmatory instrument pertaining thereto; and

c. any outstanding Deliverables contemplated or materials purchased under this contract.

3. This remedy will remain available until the end of the contract.

H.11 [***].

H.12 Transportation to Final Destination

During the course of performance under this contract, the Government may require storage of the filled drug product (FDP) before delivery to the final government location. In these circumstances, the Government will accept FDP at the contractor facility (Origin). The contractor; however, shall continue to be responsible for secure delivery of the vaccine to its final destination as identified on this contract. [***].

H.13 Validation of IP/Data

The Parties acknowledge that background intellectual property and technical data assertions have been made and evaluated by the parties. The parties agree that, should additional information relevant to these assertions become available, the parties will reevaluate said assertions as necessary in the future.

H.14 Novation

Upon Moderna, US, Inc.'s registration in the System for Award Management, the Government will, at the Contractor's request, complete a novation of this Contract to recognize Moderna US, Inc. as a counterparty instead of Moderna TX, Inc. This novation will be completed through a modification executed by the Government that identifies Moderna US, Inc. as the contracting party for all purposes as if it had originally executed the Contract.

H.15 Base & Option 1 Delivery Acceleration

In an effort to accelerate production of the mRNA-1273 vaccine, [***] within the Option 1 period via a Modification to the contract. If these manufacturing slots are

successfully utilized, [***] above what was projected by Moderna and assumed within the price per dose for the doses of mRNA-1273 vaccine delivered in the Base Period and Option 1. However, because the Government is funding the additional slots within the Base and Option 1 periods in order to accelerate production, the Government is entitled to an adjustment under the conditions outlined. The Government and Moderna agree to the following:

1. If the Government exercises Option 2 (NLT 15 May):

a. Moderna will reduce the cost of Option 2 by \$[***] for each successfully accelerated drug product fill under the Base Period ([***) and \$[***] for each successfully accelerated drug product fill under Option 1 ([***)).

2. If the Government does not exercise Option 2 (NLT 15 May):

a. In the event Moderna timely cancels the manufacturing slots and/or is able to otherwise fully utilize the slots originally reserved for production in the Option 2 period, Moderna agrees to credit the Government \$[***] for [***] and \$[***] for [***]. In no case shall the number of drug product manufacturing slots credited exceed the number of successfully accelerated drug product manufacturing fills under the Base Period and Option 1. It is understood that Moderna will make all good-faith efforts to fill reserved slots or cancel reservations in a timely manner (i.e. within the time period required by the subcontractor).

b. In the event that Moderna is unable to fill those reserved slots (i.e. due to lack of demand) and cancels slots, Moderna shall be entitled to recoup those reservation cancellation costs from the USG. The process is outlined as follows:

1.) Moderna shall submit documentation to the USG of the following:

- i.) Cancellation notice to the subcontractor,
- ii.) The basis of the cancellation, and
- iii.) Cancellation fees incurred.

2.) Moderna shall reduce credits to the USG under paragraph 2a) of this clause, IAW agreed cancellation costs incurred.

3.) Bi-lateral agreement of the final credit shall be included in a modification to the contract. Net credit shall be deducted from final payments under the contract.

H.16 Delivery Schedule, as revised 11Feb2021 via modification P00004

[***].

H.17 Post-Termination Disposition of Undelivered Product

For the avoidance of doubt, if the USG elects to terminate the exercised CLINs prior to acceptance and delivery in full of the required quantities of mRNA-1273, Moderna will be free to direct any unaccepted/undelivered supplies of mRNA-1273 to customers other than the USG, at its discretion, without further obligation of either party with regard to such unaccepted/undelivered supplies of mRNA-1273. The contract will be bilaterally modified to decrease the quantities by the agreed upon volume.

H.18 [*]**

In order to facilitate projections and invoicing, the Government shall provide or direct a third party ([**]) to provide to Moderna (1) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; (2) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; and (3) the number of [**] remaining in inventory and available for upcoming shipments. This information will be provided to Moderna at a frequency of at least twice monthly.

For each 8.0mL fill volume (1600mcg) vial of vaccine shipped with a [**].

Both parties acknowledge that the delivery schedule is based on an [**] 8.0mL fill volume (1600mcg) vial delivered. In accordance with the agreed approach for invoicing and counting doses toward Moderna's delivery requirement, [**]. Specifically for purposes of adhering to the scheduled delivery dates set forth in this contract for the Base Period, Option 1 and Option 2, schedule shall be deemed to have been met once doses are released by Moderna and are available for order.

H.19 Product [] (as added via P00018)**

Specific to CLINs 3001 and 4001, Moderna will deliver to the Government [**]:

- A) Adult Primary Series (mRNA1273 or other, as determined by EUA/BLA and any related supplement or amendment thereto accepted and authorized/licensed by FDA and mutually agreed upon; [**])
- B) [**]
- C) [**]

For avoidance of doubt, all doses delivered to the Government must be suitable for use in the United States pursuant to an active EUA or approved BLA at the time of product delivery. [**].

If US regulatory authorities determine there is a need for an updated vaccine containing one or more variant mRNA sequences for any reason, including improved efficacy against new or emerging virus strains, the Parties agree to work together in good faith to discuss any such situation and any potential impact on this contract. [**].

Both parties acknowledge that the EUA for mRNA1273 may be expanded such that doses procured under this contract may have utility beyond the currently authorized indications/populations, and in the event of any such expansion, the Government will not be restricted hereunder from use of mRNA1273 in accordance with the full scope of any FDA authorization and CDC recommendation to the extent consistent with the Government's obligations under Section H.8 and the terms of Section H.20.

The Government and Moderna agree that the total monthly delivery quantities for CLIN 3001 and 4001 will follow the following Delivery Schedule:

[**]

The Government and Moderna agree as follows:

- [**].
- *Sale of doses to the African Union.* The Government is agreeing to defer delivery of 33,000,000 doses previously scheduled for delivery in December and February to facilitate Moderna's supply of 50,000,000 doses of mRNA1273 to the African Union (AU) at a notforprofit price.

- [***].

EUA Wind Down. It is anticipated that all mRNA1273 under this contract will be delivered in accordance with an active EUA. If a BLA is issued during the term of this Contract for the mRNA1273 vaccine, the Government and Moderna shall discuss an appropriate transition of mRNA1273 to BLA which will include that any doses subsequently provided to the Government under this Contract are appropriately labeled and are otherwise suitable for use in the United States under the terms of the EUA (before expiration) or the BLA.

H.20 Donation of Excess Product

- a. If the Government determines that a quantity of doses of mRNA-1273 supplied to the Government under this contract is no longer needed by the Government, the Government may donate such doses to a foreign nation or non- governmental organization (NGO) facilitating donation to a foreign nation, subject to the remainder of this Clause H.20. The Government shall notify Contractor in writing prior to any proposed donation to a foreign nation or NGO, which notice will include [***].
- b. Contractor must verify in writing that all of the required conditions below are met before any such donation is made, [***]:
- (i) [***];
 - (ii) [***];
 - (iii) [***]; and
 - (iv) [***].
- c. The Government's donations will be from supplies of vaccine delivered to and accepted by the Government. To the extent the Government commits to deliver doses that have not yet been physically delivered to the Government, such donation will not occur until such doses have been delivered to the Government. The Government will be responsible for delivery of the donated doses to, and coordination of delivery with, the receiving foreign nation or NGO, as applicable. The Government or the receiving foreign nation or NGO, as applicable, will (i) satisfy all customs shipping requirements for import and export of the product; and (ii) as the exporter, file any required FDA export notifications. To the extent not already provided to the Government, the Contractor will provide all information necessary to complete any requirements identified in this paragraph in advance of shipment.
- d. When the conditions above are met for any donation, the Parties will [***].
-

e. [***].

f. Shipment of any donated doses under this Article does not constitute a violation of the Defense Production Act.

(End of Summary of Changes)

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE OF PAGES

1 14

2. AMENDMENT/MODIFICATION NO.

3. EFFECTIVE DATE

4. REQUISITION/PURCHASE REQ. NO.

5. PROJECT NO.(If applicable)

P00019

15-NOV-2021

See Schedule

6. ISSUED BY CODE

W58P05

7. ADMINISTERED BY (If other than item 6) CODE

S2206A

ACC-APG - COVID RESPONSE - W58P05
 6472 INTEGRITY COURT (BUILDING 4401)
 ABERDEEN PROVING GROUND MD 21005-3013

DCMA BOSTON
 495 SUMMER STREET
 BOSTON MA 02210-2138

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)

9A. AMENDMENT OF SOLICITATION NO.

9B. DATED (SEE ITEM 11)

MODERNA US, INC.

[***]

200 TECHNOLOGY SQ

CAMBRIDGE MA 02139-3578

X

10A. MOD. OF CONTRACT/ORDER NO.
W911QY20C0100

X

10B. DATED (SEE ITEM 13)

CODE 8PTM0

FACILITY CODE

09-Aug-2020

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Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods:

(a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)**13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS.**

IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

- A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
- B. THE ABOVE NUMBERED CONTRACT /ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).
- C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
- D. OTHER (Specify type of modification and authority)

X

E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.**14. DESCRIPTION OF AMENDMENT /MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)**

Modification Control Number: [***]

See Block 14 Continuation Page

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)

Shaun Ryan, SVP & Deputy General Counsel

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)

[***]

TEL: [***] EMAIL: [***]

15B. CONTRACT OR/OFFEROR

/s/ Shaun Ryan

(Signature of person authorized to sign)

15C. DATE SIGNED

11/10/21

16B. UNITED STATES OF AMERICA

BY [***]

(Signature of Contracting Officer)

16C. DATE SIGNED

15-NOV-2021

EXCEPTION TO SF 30
 APPROVED BY OIRM 11-84

30-105-04

STANDARD FORM 30 (Rev. 10-83)
 Prescribed by GSA
 FAR (48 CFR) 53.243

[illegible]

H.2 Substitution of Key Personnel

The Contractor agrees to assign to the contract those persons whose resumes/CVs were submitted with the proposal who are necessary to fill the requirements of the contract. No substitutions shall be made except in accordance with this clause.

All requests for substitution must provide a detailed explanation of the circumstance necessitating the proposed substitution, a complete resume for the proposed substitute and any other information requested by the contracting officer to approve or disapprove the proposed substitution. All proposed substitutes must have qualifications that are equal to or higher than the qualifications of the person to be replaced. The contracting officer or authorized representative will evaluate such requests and promptly notify the contractor of his approval or disapproval thereof.

H.3 Disclosure of Information:

Performance under this contract may require the Contractor to access non-public data and information proprietary to a Government agency, another Government Contractor or of such nature that its dissemination or use other than as specified in the work statement would be adverse to the interests of the Government or others. Neither the Contractor, nor Contractor personnel, shall divulge nor release data nor information developed or obtained under performance of this contract, except authorized by Government personnel or upon written approval of the CO which the KO will provide in accordance with OWS or other Government policies and/or guidance. The Contractor shall not use, disclose, or reproduce proprietary data that bears a restrictive legend, other than as specified in this contract, or any information at all regarding this agency.

The Contractor shall comply with all applicable Government requirements for protection of non-public information. Unauthorized disclosure of nonpublic information is prohibited by the Government's rules. Unauthorized disclosure may result in termination of the contract, replacement of a Contractor employee, or other appropriate redress. Neither the Contractor nor the Contractor's employees shall disclose or cause to be disseminated, any information concerning the operations of the activity, which could result in, or increase the likelihood of, the possibility of a breach of the activity's security or interrupt the continuity of its operations.

No information related to data obtained under this contract shall be released or publicized without the prior written consent of the COR, whose approval shall not be unreasonably withheld, conditioned, or delayed, provided that no such consent is required to comply with any law, rule, regulation, court ruling or similar order; for submission to any government entity; for submission to any securities exchange on which the Contractor's (or its parent corporation's) securities may be listed for trading; or to third parties relating to securing, seeking, establishing or maintaining regulatory or other legal approvals or compliance, financing and capital raising activities, or mergers, acquisitions, or other business transactions. The exceptions identified in this paragraph apply to all disclosures under this Section H.3 except to the extent that a disclosure is otherwise prohibited by law.

H.4 Publication and Publicity

The contractor shall not release any reports, manuscripts, press releases, or abstracts about the work being performed under this contract without written notice in advance to the Government.

a. Unless otherwise specified in this contract, the contractor may publish the results of its work under this contract. The contractor shall promptly send a copy of each submission to the COR for security review prior to submission. The contractor shall also inform the COR when the abstract article or other publication is published, and furnish a copy of it as finally published.

- b. Unless authorized in writing by the CO, the contractor shall not display the DoD logo including Operating Division or Staff Division logos on any publications.
- c. The contractor shall not reference the products(s) or services(s) awarded under this contract in commercial advertising, as defined in FAR 31.205-1, in any manner which states or implies DoD approval or endorsement of the product(s) or service(s) provided.
- d. The contractor shall include this clause, including this section (d) in all subcontracts where the subcontractor may propose publishing the results of its work under the subcontract. The contractor shall acknowledge the support of the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority whenever publicizing the work under this contract in any media by including an acknowledgement substantially as follows:

“This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract Number W911QY-20-C-0100.”

H.5 Confidentiality of Information

- a. Confidential information, as used in this article, means non-public information or data of a personal nature about an individual, or proprietary information or data submitted by or pertaining to an institution or organization.
- b. The Contracting Officer and the Contractor may, by mutual consent, identify elsewhere in this contract specific information and/or categories of information which the Government will furnish to the Contractor or that the Contractor is expected to generate which is confidential. Similarly, the Contracting Officer and the Contractor may, by mutual consent, identify such confidential information from time to time during the performance of the contract. Failure to agree will be settled pursuant to the “Disputes” clause.
- c. If it is established elsewhere in this contract that information to be utilized under this contract, or a portion thereof, is subject to the Privacy Act, the Contractor will follow the rules and procedures of disclosure set forth in the Privacy Act of 1974, 5 U.S.C. 552a, and implementing regulations and policies, with respect to systems of records determined to be subject to the Privacy Act.
- d. Confidential information, as defined in paragraph (a) of this article, shall not be disclosed without the prior written consent of the individual, institution, or organization.
- e. Whenever the Contractor is uncertain with regard to the proper handling of material under the contract, or if the material in question is subject to the Privacy Act or is confidential information subject to the provisions of this article, the Contractor shall obtain a written determination from the Contracting Officer prior to any release, disclosure, dissemination, or publication.
- f. Contracting Officer Determinations will reflect the result of internal coordination with appropriate program and legal officials.
- g. The provisions of paragraph (d) of this article shall not apply to conflicting or overlapping provisions in other Federal, State or local laws.

ALL REQUIREMENTS OF THIS SECTION H.5 MUST BE PASSED TO ALL SUB-CONTRACTOR.

H.6 Regulatory Rights

This contract involves supply of a product that requires FDA pre-market approval or clearance before commercial authorization. Contractor is seeking FDA authorization or clearance for the commercialization of mRNA-1273, Moderna vaccine for SARS-CoV-2 Coronavirus (the “Technology”). The Contractor is the Sponsor of the Regulatory Application (an investigational new drug application (IND), investigational device exemption (IDE), emergency use authorization (EUA), new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), or 510(k) pre-market notification filing (510(k)) or another regulatory filing submitted to FDA) for the technology. As the Sponsor of the Regulatory Application to FDA (as the terms “sponsor” and “applicant” are defined or used in at 21 CFR §§3.2(c), 312.5, 600.3(t), 812.2(b), 812 Subpart C, or 814.20), the Contractor has certain standing before the FDA that entitles it to exclusive communications related to the Regulatory Application.

Accordingly, the Contractor and the Government agree to the following:

a. DoD Medical Product Priority. PL 115-92 allows the DoD to request, and FDA to provide, assistance to expedite development of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing American military personnel. The contractor recognizes that only the DoD can utilize PL 115-92. As such, the contractor will work proactively with the Government to leverage this law to its maximum potential under this contract. The contractor shall submit Public Law 115-92 Sponsor Authorization Letter that will be delivered to the designated OWS POC(s) within [***] of award.

b. [***].

H.7 Performance Based Payment Liquidated under Termination

Performance Based Payments (PBPs) have been authorized as a method of financing under this contract. In the event the Moderna's mRNA-1273 COVID Vaccine is unsuccessful in its bid to obtain EUA or FDA approval, the Government may issue a Termination for Convenience (T4C) in whole or in part, on this contract. Upon notice of a T4C, the contractor shall submit a termination settlement proposal, IAW FAR 52.249-2, Termination for Convenience of the Government (Fixed-Price).

H.8 Public Readiness and Emergency Preparedness (PREP) Act:

In accordance with the Public Readiness and Emergency Preparedness Act ("PREP Act"), Pub. L. No. 109-148, Division C, Section 2, as amended (codified at 42 U.S.C. § 247d-6d and 42 U.S.C. § 247d-6e), as well as the Secretary of HHS's Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 15198 (Mar. 17, 2020, effective Feb. 4, 2020), and amended on April 15, 2020, 85 Fed. Reg. 21012 (together, the "Prep Act Declaration"):

(i) This Agreement is being entered into for purposes of facilitating the manufacture, testing, development, distribution, administration, and use of "Covered Countermeasures" for responding to the COVID-19 public health emergency, in accordance with Section VI of the PREP Act Declaration;

(ii) Contractor's performance of this Agreement falls within the scope of the "Recommended Activities" for responding to the COVID-19 public health emergency, to the extent it is in accordance with Section III of the PREP Act Declaration; and

(iii) Contractor is a "Covered Person" to the extent it is a person defined in Section V of the PREP Act

Declaration.

Therefore, in accordance with Sections IV and VII of the PREP Act Declaration as well as the PREP Act (42 U.S.C. § 247d-6d), the Department of Defense contracting via assisted acquisition on behalf of the HHS, expressly acknowledges and agrees that the HHS Declaration cited above, specifically its language providing immunity from suit and liability is applicable to this acquisition as long as Contractors activities fall within the terms and conditions of the PREP Act and the PREP Act Declaration.

The Government may not use, or authorize the use of, any products or materials provided under this contract, unless such use occurs in the United States (or a U.S. territory where U.S. law applies such as embassies, military and NATO installations) and is protected from liability under a declaration issued under the PREP Act, or a successor COVID-19 PREP Act Declaration of equal or greater scope. Any use where the application of the PREP Act is in question will be discussed with Moderna prior to use and, if the parties disagree on such use, the dispute will be resolved according to the "Disputes Clause" (52.233-1)

The items and technology covered by this Contract are being developed for both civil and military applications.

H.9 [***].

H.10 Ensuring Sufficient Supply of the Product

1. In recognition of the Government's significant funding for the development and manufacturing of the product in this contract and the Government's need to provide sufficient quantities of a COVID-19 vaccine to protect the United States population, the Government shall have the remedy described in this section to ensure sufficient supply of the product to meet the needs of the public health or national security. This remedy is not available to the Government unless and until both of the following conditions ((a) and (b)) are met:

a. Moderna gives written notice, required to be submitted to the Government [***], of:

- (i) any formal management decision to terminate manufacturing of this product vaccine prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons or;
- (ii) any formal management decision to discontinue sale of this product vaccine to the Government prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons; or
- (iii) any filing that anticipates Federal bankruptcy protection; and

b. Moderna has submitted an Emergency Use Authorization application under §564 of the FD&C Act or a biologics license application provisions of §351(a) of the Public Health Service Act (PHSA).

2. If both conditions listed in section 1 occur, Moderna, upon the request of the Government, shall provide the following items necessary for the Government to pursue manufacturing of this product vaccine with a third party for exclusive sale to the U.S. Government:

- a. a writing evidencing a non-exclusive, nontransferable, irrevocable (except for cause), royalty-free paid-up license to practice or have practiced for or on behalf of the U.S. Government any Moderna Background Patent, Copyright, other Moderna Intellectual Property, Moderna Know-How, Moderna Technical Data rights necessary to manufacture doses of the mRNA-1273 vaccine;
- b. necessary FDA regulatory filings or authorizations owned or controlled by Moderna related to this product vaccine and any confirmatory instrument pertaining thereto; and
- c. any outstanding Deliverables contemplated or materials purchased under this contract.

3. This remedy will remain available until the end of the contract.

H.11 [***].

H.12 Transportation to Final Destination

During the course of performance under this contract, the Government may require storage of the filled drug product (FDP) before delivery to the final government location. In these circumstances, the Government will accept FDP at the contractor facility (Origin). The contractor; however, shall continue to be responsible for secure delivery of the vaccine to its final destination as identified on this contract. [***].

H.13 Validation of IP/Data

The Parties acknowledge that background intellectual property and technical data assertions have been made and evaluated by the parties. The parties agree that, should additional information relevant to these assertions become available, the parties will reevaluate said assertions as necessary in the future.

H.14 Novation

Upon Moderna, US, Inc.'s registration in the System for Award Management, the Government will, at the Contractor's request, complete a novation of this Contract to recognize Moderna US, Inc. as a counterparty instead

of Moderna TX, Inc. This novation will be completed through a modification executed by the Government that identifies Moderna US, Inc. as the contracting party for all purposes as if it had originally executed the Contract.

H.15 Base & Option 1 Delivery Acceleration

In an effort to accelerate production of the mRNA-1273 vaccine, [***] within the Option 1 period via a Modification to the contract. If these manufacturing slots are successfully utilized, [***] above what was projected by Moderna and assumed within the price per dose for the doses of mRNA-1273 vaccine delivered in the Base Period and Option 1. However, because the Government is funding the additional slots within the Base and Option 1 periods in order to accelerate production, the Government is entitled to an adjustment under the conditions outlined. The Government and Moderna agree to the following:

1. If the Government exercises Option 2 (NLT 15 May):

a. Moderna will reduce the cost of Option 2 by \$[***] for each successfully accelerated drug product fill under the Base Period ([**]) and \$[***] for each successfully accelerated drug product fill under Option 1 ([**]).

2. If the Government does not exercise Option 2 (NLT 15 May):

a. In the event Moderna timely cancels the manufacturing slots and/or is able to otherwise fully utilize the slots originally reserved for production in the Option 2 period, Moderna agrees to credit the Government \$[***] for [**] and \$[***] for [**]. In no case shall the number of drug product manufacturing slots credited exceed the number of successfully accelerated drug product manufacturing fills under the Base Period and Option 1. It is understood that Moderna will make all good-faith efforts to fill reserved slots or cancel reservations in a timely manner (i.e. within the time period required by the subcontractor).

b. In the event that Moderna is unable to fill those reserved slots (i.e. due to lack of demand) and cancels slots, Moderna shall be entitled to recoup those reservation cancellation costs from the USG. The process is outlined as follows:

1.) Moderna shall submit documentation to the USG of the following:

- i.) Cancellation notice to the subcontractor,
- ii.) The basis of the cancellation, and
- iii.) Cancellation fees incurred.

2.) Moderna shall reduce credits to the USG under paragraph 2a) of this clause, IAW agreed cancellation costs incurred.

3.) Bi-lateral agreement of the final credit shall be included in a modification to the contract. Net credit shall be deducted from final payments under the contract.

H.16 Delivery Schedule, as revised 11Feb2021 via modification P00004

[***].

H.17 Post-Termination Disposition of Undelivered Product

For the avoidance of doubt, if the USG elects to terminate the exercised CLINs prior to acceptance and delivery in full of the required quantities of mRNA-1273, Moderna will be free to direct any unaccepted/undelivered supplies of mRNA-1273 to customers other than the USG, at its discretion, without further obligation of either party with regard to such unaccepted/undelivered supplies of mRNA-1273. The contract will be bilaterally modified to decrease the quantities by the agreed upon volume.

H.18 [*]**

In order to facilitate projections and invoicing, the Government shall provide or direct a third party ([**]) to provide to Moderna (1) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; (2) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; and (3) the number of [**] remaining in inventory and available for upcoming shipments. This information will be provided to Moderna at a frequency of at least twice monthly.

For each 8.0mL fill volume (1600mcg) vial of vaccine shipped with a [**].

Both parties acknowledge that the delivery schedule is based on an [**] 8.0mL fill volume (1600mcg) vial delivered. In accordance with the agreed approach for invoicing and counting doses toward Moderna's delivery requirement, [**]. Specifically for purposes of adhering to the scheduled delivery dates set forth in this contract for the Base Period, Option 1 and Option 2, schedule shall be deemed to have been met once doses are released by Moderna and are available for order.

H.19 Product [] (as added via P00018)**

Specific to CLINs 3001 and 4001, Moderna will deliver to the Government [**]:

- a. Adult Primary Series (mRNA-1273 or other, as determined by EUA/BLA and any related supplement or amendment thereto accepted and authorized/licensed by FDA and mutually agreed upon; [**])
-

b. [***]

c. [***]

For avoidance of doubt, all doses delivered to the Government must be suitable for use in the United States pursuant to an active EUA or approved BLA at the time of product delivery. [***].

If US regulatory authorities determine there is a need for an updated vaccine containing one or more variant mRNA sequences for any reason, including improved efficacy against new or emerging virus strains, the Parties agree to work together in good faith to discuss any such situation and any potential impact on this contract. [***].

Both parties acknowledge that the EUA for mRNA-1273 may be expanded such that doses procured under this contract may have utility beyond the currently authorized indications/populations, and in the event of any such expansion, the Government will not be restricted hereunder from use of mRNA-1273 in accordance with the full scope of any FDA authorization and CDC recommendation to the extent consistent with the Government's obligations under Section H.8 and the terms of Section H.20.

The Government and Moderna agree that the total monthly delivery quantities for CLIN 3001 and 4001 will follow the following Delivery Schedule:

[***]

The Government and Moderna agree as follows:

- [***].
- *Sale of doses to the African Union.* The Government is agreeing to defer delivery of 33,000,000 doses previously scheduled for delivery in December and February to facilitate Moderna's supply of 50,000,000 doses of mRNA-1273 to the African Union (AU) at a not-for-profit price.
- [***].

EUA Wind Down. It is anticipated that all mRNA-1273 under this contract will be delivered in accordance with an active EUA. If a BLA is issued during the term of this Contract for the mRNA-1273 vaccine, the Government and Moderna shall discuss an appropriate transition of mRNA-1273 to BLA which will include that any doses subsequently provided to the Government under this Contract are appropriately labeled and are otherwise suitable for use in the United States under the terms of the EUA (before expiration) or the BLA.

H.20 Donation of Excess Product

a. If the Government determines that a quantity of doses of mRNA-1273 supplied to the Government under this contract is no longer needed by the Government, the Government may donate such doses to a foreign nation or nongovernmental organization (NGO) facilitating donation to a foreign nation, subject to the remainder of this Clause H.20. The Government shall notify Contractor in writing prior to any proposed donation to a foreign nation or NGO, which notice will include [***].

b. Contractor must verify in writing that all of the required conditions below are met before any such donation is made, [***]:

(i) [***];

(ii) [***];

(iii) [***]; and

(iv) [***].

c. Additionally, the Government may donate product for use in the clinical study to be conducted pursuant to the Clinical Trial Agreement (as amended on October 28, 2021) between The National Institute of Allergy and Infectious Disease (“NIAID”) and the South African Medical Research Council (“SAMRC”) under Protocol CoVPN 3008 (the “CoVPN 3008 Study”), subject to the Government’s having a binding written agreement(s) in place with the sponsor that satisfies the conditions set forth below in this clause (c):

- (i) [***],
 - (ii) [***];
 - (iii) [***].
 - (iv) [***];
 - (v) [***];
 - (vi) [***];
 - (vii) [***];
 - (viii) [***];
 - (ix) [***]; and
 - (x) [***].
-

d. The Government's donations will be from supplies of vaccine delivered to and accepted by the Government. To the extent the Government commits to deliver doses that have not yet been physically delivered to the Government, such donation will not occur until such doses have been delivered to the Government. The Government will be responsible for delivery of the donated doses to, and coordination of delivery with, the receiving foreign nation, clinical study sponsor, or NGO, as applicable. The Government or the receiving foreign nation, clinical study sponsor, or NGO, as applicable, will (i) satisfy all customs shipping requirements for import and export of the product; and (ii) as the exporter, file any required FDA export notifications. To the extent not already provided to the Government, the Contractor will provide all information necessary to complete any requirements identified in this paragraph in advance of shipment.

e. When the conditions above are met for any donation, the Parties will [***].

f. [***].

g. Shipment of any donated doses under this Article does not constitute a violation of the Defense Production Act.

H.21 CDC Healthcare Provider List

To ensure timely communication is provided to health care providers, the USG has provided Moderna the mailing list for the Centers for Disease Control and Prevention (CDC) healthcare providers administering Moderna's vaccine and boosters in order for Moderna to send information regarding boosters that were authorized by the FDA on October 20, 2021. Moderna agrees to the terms below of the handling of the CDC Healthcare Provider List.

1. Moderna shall use the CDC Healthcare Provider List only for the express purpose of the specific mailing regarding Moderna's FDA-authorized booster product/EUA expansion;
2. Moderna shall not share or provide this list to any outside parties other than those who are supporting this specific mailing; and
3. Moderna shall delete (and require any other parties to delete) the list once they have completed the mailing.

SECTION J - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

The following have been modified:

Document Type	Description	Page #	Date
Exhibit A	CDRLs	15	11 February 2021
Exhibit B	Donation of Excess Product	8	1 November 2021
Attachment 0001	Supply Chain Resiliency Plan for CDRL A010	3	23 July 2020
Attachment 0002	Security Plan	7	23 July 2020
Attachment 0003	Dose Tracking Template Draft Moderna	Excel	15 July 2020
Attachment 0004	Data Rights	3	7 August 2020
Attachment 0005	[***]	2	7 August 2020
Attachment 0006	ModernaTx, Inc. Background Intellectual Property	3	6 August 2020
Attachment 0007	Performance Base Payment Milestone Schedule	1	14 June 2021
Attachment 0008	Performance Base Payment Milestone Billing Plan	16	3 September 2021
Attachment 0009	HRPAS Moderna Letter	1	3 September 2020

(End of Summary of Changes)

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE OF PAGES

1 16

2. AMENDMENT/MODIFICATION NO.

3. EFFECTIVE DATE

4. REQUISITION/PURCHASE REQ. NO.

5. PROJECT NO.(If applicable)

P00020

22 DEC 2021

See Schedule

6. ISSUED BY CODE

W58P05

7. ADMINISTERED BY (If other than item 6) CODE

S2206A

ACC-APG - COVID RESPONSE - W58P05
 6472 INTEGRITY COURT (BUILDING 4401)
 ABERDEEN PROVING GROUND MD 21005-3013

DCMA BOSTON
 495 SUMMER STREET
 BOSTON MA 02210-2138

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)

9A. AMENDMENT OF SOLICITATION NO.

9B. DATED (SEE ITEM 11)

MODERNA US, INC.

[***]

200 TECHNOLOGY SQ

CAMBRIDGE MA 02139-3578

X

10A. MOD. OF CONTRACT/ORDER NO.

W911QY20C0100

X

10B. DATED (SEE ITEM 13)

CODE 8PTM0

FACILITY CODE

09-Aug-2020

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods:

(a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)**13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS.**

IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

- A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
- B. THE ABOVE NUMBERED CONTRACT /ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).
- C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
- D. OTHER (Specify type of modification and authority)

X

E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.**14. DESCRIPTION OF AMENDMENT /MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)**

Modification Control Number: [***]

See Block 14 Continuation Page

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)

Shaun Ryan, SVP & Deputy General Counsel

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)

[***]

TEL: [***] EMAIL: [***]

15B. CONTRACT OR/OFFEROR

/s/ Shaun Ryan

(Signature of person authorized to sign)

15C. DATE SIGNED

12/21/2021

16B. UNITED STATES OF AMERICA

BY [***]

(Signature of Contracting Officer)

16C. DATE SIGNED

22 December 2021

EXCEPTION TO SF 30
 APPROVED BY OIRM 11-84

30-105-04

STANDARD FORM 30 (Rev. 10-83)
 Prescribed by GSA
 FAR (48 CFR) 53.243

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION SF 30 - BLOCK 14 CONTINUATION PAGE

The following have been added by full text: P00020

OBLIGATION AMOUNT: \$0.00

- a. The purpose of this modification (P00020) is to:
- Update Section G Contracting Officer and Government Technical Point of Contract (FAR 43.103(b))
 - Update Moderna Contractor's Contract Administration in Section G and Key Personnel in H.1 (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties)
 - Update Exhibit B as outlined in clause H.20 with donation information for multiple recipients identified (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties).
- b. This modification was requested by the program office to meet the Government's mission requirements.
- c. The total contract value and total funded amount remain unchanged.

SECTION G - CONTRACT ADMINISTRATION DATA

The following have been modified:

G.1 GOVERNMENT CONTRACT ADMINISTRATION

In no event shall any understanding or agreement, contract modification, change order, or other matter in deviation from the terms of this contract between the Contractor and a person other than the Contracting Officer be effective or binding upon the Government. All such actions must be formalized by a proper contractual document executed by the Contracting Officer.

Procuring Contracting Officer:

[***]

Joint COVID-19 Response Division
US Army Contracting Command
6472 Integrity Court (Building 4401)
Aberdeen Proving Ground, MD 21005-3013

Contract Specialist:

[***]

Joint COVID-19 Response Division
US Army Contracting Command

6472 Integrity Court (Building 4401)
Aberdeen Proving Ground, MD 21005-3013

Contract Specialist:
[***]
Joint COVID-19 Response Division
US Army Contracting Command
6472 Integrity Court (Building 4401)
Aberdeen Proving Ground, MD 21005-3013

G.2 GOVERNMENT TECHNICAL POINT OF CONTACT

[***]
Biologist/Project Officer
200 C Street, SW
Washington, DC 20201

G.3 CONTRACTOR'S CONTRACT ADMINISTRATION

[***]
Moderna US, Inc.
200 Technology SQ.
Cambridge, MA 02139-3578

G.4 PLACES OF PERFORMANCE

Moderna US, Inc.
200 Technology SQ.
Cambridge, MA 02139-3578

G.5 NOTIFICATION OF REVISIONS AND CHANGE

Notification of revision or changes to names or email addresses will be provided by official correspondence from the PCO/ACO or office of the PCO/ACO in lieu of a contract modification. This does not apply to any such revisions or changes in the event this contract includes a key personnel clause.

G.6 PERFORMANCE BASED PAYMENT

Performance-based payments (PBP) are authorized under this contract in accordance with FAR 52.232-32. The contractor shall bill for the PBP upon achievement of the completion criteria identified in Attachment 0007, Performance-based Payment Milestone Table dated 4 May 2021. Upon achievement of the completion criteria, the contractor shall bill for the PBP for the base and each option IAW the following schedule:

CLIN	Period	Amount	
0001AA	BASE	\$90,210,000	
0001AB	BASE	\$132,308,000	
0001AC	BASE	\$180,420,000	
0001AD	BASE	\$198,462,000	
	TOTAL		\$601,400,000
[***]	[***]	\$[***]	
[***]	[***]	\$[***]	
[***]	[***]	\$[***]	
	TOTAL		\$[***]
[***]	[***]	\$[***]	
[***]	[***]	\$[***]	
[***]	[***]	\$[***]	

	TOTAL	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
	TOTAL	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
[***]	[***]	\$[***]
	TOTAL	\$[***]

Delivery Invoicing: PBPs are a type of contract financing and are recouped by the Government through deductions of payments otherwise due to the contractor for the partial or complete delivery of contract items. The deductions are made by applying a liquidation rate to the price of delivered contract items. Attachment 0008, Performance- based Payment Milestone Billing Plan, identifies the contractor invoicing schedule for liquidation. The contractor shall submit all invoices IAW Attachment 0008.

SECTION H - SPECIAL CONTRACT REQUIREMENTS

The following have been modified:

H.1 Key Personnel

Any key personnel specified in this contract are considered to be essential to work performance. At least thirty (30) calendar days prior to the Contractor voluntarily diverting any of the specified individuals to other programs or contracts the Contractor shall notify the Contracting Officer and shall submit a justification for the diversion or replacement and a request to replace the individual. The request must identify the proposed replacement and provide an explanation of how the replacement's skills, experience, and credentials meet or exceed the requirements of the contract (including, when applicable, Human Subjects Testing requirements). If the employee of the Contractor is terminated for cause or separates from the Contractor voluntarily with less than thirty (30) calendar-day notice, the Contractor shall provide the maximum notice practicable under the circumstances. The Contractor shall not divert, replace, or announce any such change to key personnel without the written consent of the Contracting Officer. The contract will be modified to add or delete key personnel as necessary to reflect the agreement of the parties. The following individuals are determined to be key personnel:

Name	Title
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

H.2 Substitution of Key Personnel

The Contractor agrees to assign to the contract those persons whose resumes/CVs were submitted with the proposal who are necessary to fill the requirements of the contract. No substitutions shall be made except in accordance with this clause.

All requests for substitution must provide a detailed explanation of the circumstance necessitating the proposed substitution, a complete resume for the proposed substitute and any other information requested by the contracting officer to approve or disapprove the proposed substitution. All proposed substitutes must have qualifications that are equal to or higher than the qualifications of the person to be replaced. The contracting officer or authorized representative will evaluate such requests and promptly notify the contractor of his approval or disapproval thereof.

H.3 Disclosure of Information:

Performance under this contract may require the Contractor to access non-public data and information proprietary to a Government agency, another Government Contractor or of such nature that its dissemination or use other than as specified in the work statement would be adverse to the interests of the Government or others. Neither the Contractor, nor Contractor personnel, shall divulge nor release data nor information developed or obtained under performance of this contract, except authorized by Government personnel or upon written approval of the CO which the KO will provide in accordance with OWS or other Government policies and/or guidance. The Contractor shall not use, disclose, or reproduce proprietary data that bears a restrictive legend, other than as specified in this contract, or any information at all regarding this agency.

The Contractor shall comply with all applicable Government requirements for protection of non-public information. Unauthorized disclosure of nonpublic information is prohibited by the Government's rules. Unauthorized disclosure may result in termination of the contract, replacement of a Contractor employee, or other appropriate redress. Neither the Contractor nor the Contractor's employees shall disclose or cause to be disseminated, any information concerning the operations of the activity, which could result in, or increase the likelihood of, the possibility of a breach of the activity's security or interrupt the continuity of its operations.

No information related to data obtained under this contract shall be released or publicized without the prior written consent of the COR, whose approval shall not be unreasonably withheld, conditioned, or delayed, provided that no such consent is required to comply with any law, rule, regulation, court ruling or similar order; for submission to any government entity' for submission to any securities exchange on which the Contractor's (or its parent corporation's) securities may be listed for trading; or to third parties relating to securing, seeking, establishing or maintaining regulatory or other legal approvals or compliance, financing and capital raising activities, or mergers, acquisitions, or other business transactions. The exceptions identified in this paragraph apply to all disclosures under this Section H.3 except to the extent that a disclosure is otherwise prohibited by law.

H.4 Publication and Publicity

The contractor shall not release any reports, manuscripts, press releases, or abstracts about the work being performed under this contract without written notice in advance to the Government.

- a. Unless otherwise specified in this contract, the contractor may publish the results of its work under this contract. The contractor shall promptly send a copy of each submission to the COR for security review prior to submission. The contractor shall also inform the COR when the abstract article or other publication is published, and furnish a copy of it as finally published.
 - b. Unless authorized in writing by the CO, the contractor shall not display the DoD logo including Operating Division or Staff Division logos on any publications.
 - c. The contractor shall not reference the products(s) or services(s) awarded under this contract in commercial advertising, as defined in FAR 31.205-1, in any manner which states or implies DoD approval or endorsement of the product(s) or service(s) provided.
 - d. The contractor shall include this clause, including this section (d) in all subcontracts where the subcontractor may propose publishing the results of its work under the subcontract. The contractor shall acknowledge the support of the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority whenever publicizing the work under this contract in any media by including an acknowledgement substantially as follows:
-

“This project has been funded in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract Number W911QY-20-C-0100.”

H.5 Confidentiality of Information

- a. Confidential information, as used in this article, means non-public information or data of a personal nature about an individual, or proprietary information or data submitted by or pertaining to an institution or organization.
- b. The Contracting Officer and the Contractor may, by mutual consent, identify elsewhere in this contract specific information and/or categories of information which the Government will furnish to the Contractor or that the Contractor is expected to generate which is confidential. Similarly, the Contracting Officer and the Contractor may, by mutual consent, identify such confidential information from time to time during the performance of the contract. Failure to agree will be settled pursuant to the “Disputes” clause.
- c. If it is established elsewhere in this contract that information to be utilized under this contract, or a portion thereof, is subject to the Privacy Act, the Contractor will follow the rules and procedures of disclosure set forth in the Privacy Act of 1974, 5 U.S.C. 552a, and implementing regulations and policies, with respect to systems of records determined to be subject to the Privacy Act.
- d. Confidential information, as defined in paragraph (a) of this article, shall not be disclosed without the prior written consent of the individual, institution, or organization.
- e. Whenever the Contractor is uncertain with regard to the proper handling of material under the contract, or if the material in question is subject to the Privacy Act or is confidential information subject to the provisions of this article, the Contractor shall obtain a written determination from the Contracting Officer prior to any release, disclosure, dissemination, or publication.
- f. Contracting Officer Determinations will reflect the result of internal coordination with appropriate program and legal officials.
- g. The provisions of paragraph (d) of this article shall not apply to conflicting or overlapping provisions in other Federal, State or local laws.

ALL REQUIREMENTS OF THIS SECTION H.5 MUST BE PASSED TO ALL SUB-CONTRACTOR.

H.6 Regulatory Rights

This contract involves supply of a product that requires FDA pre-market approval or clearance before commercial authorization. Contractor is seeking FDA authorization or clearance for the commercialization of mRNA-1273, Moderna vaccine for SARS-CoV-2 Coronavirus (the “Technology”). The Contractor is the Sponsor of the Regulatory Application (an investigational new drug application (IND), investigational device exemption (IDE), emergency use authorization (EUA), new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), or 510(k) pre-market notification filing (510(k)) or another regulatory filing submitted to FDA) for the technology. As the Sponsor of the Regulatory Application to FDA (as the terms “sponsor” and “applicant” are defined or used in at 21 CFR §§3.2(c), 312.5, 600.3(t), 812.2(b), 812 Subpart C, or 814.20), the Contractor has certain standing before the FDA that entitles it to exclusive communications related to the Regulatory Application.

Accordingly, the Contractor and the Government agree to the following:

a. DoD Medical Product Priority. PL 115-92 allows the DoD to request, and FDA to provide, assistance to expedite development of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing American military personnel. The contractor recognizes that only the DoD can utilize PL 115-92. As such, the contractor will work proactively with the Government to leverage this law to its maximum potential under this contract. The contractor shall submit Public Law 115-92 Sponsor Authorization Letter that will be delivered to the designated OWS POC(s) within [***] award.

b. [***].

H.7 Performance Based Payment Liquidated under Termination

Performance Based Payments (PBPs) have been authorized as a method of financing under this contract. In the event the Moderna's mRNA-1273 COVID Vaccine is unsuccessful in its bid to obtain EUA or FDA approval, the Government may issue a Termination for Convenience (T4C) in whole or in part, on this contract. Upon notice of a T4C, the contractor shall submit a termination settlement proposal, IAW FAR 52.249-2, Termination for Convenience of the Government (Fixed-Price).

H.8 Public Readiness and Emergency Preparedness (PREP) Act:

In accordance with the Public Readiness and Emergency Preparedness Act ("PREP Act"), Pub. L. No. 109-148, Division C, Section 2, as amended (codified at 42 U.S.C. § 247d-6d and 42 U.S.C. § 247d-6e), as well as the Secretary of HHS's Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 15198 (Mar. 17, 2020, effective Feb. 4, 2020), and amended on April 15, 2020, 85 Fed. Reg. 21012 (together, the "Prep Act Declaration"):

(i) This Agreement is being entered into for purposes of facilitating the manufacture, testing, development, distribution, administration, and use of "Covered Countermeasures" for responding to the COVID-19 public health emergency, in accordance with Section VI of the PREP Act Declaration;

(ii) Contractor's performance of this Agreement falls within the scope of the "Recommended Activities" for responding to the COVID-19 public health emergency, to the extent it is in accordance with Section III of the PREP Act Declaration; and

(iii) Contractor is a "Covered Person" to the extent it is a person defined in Section V of the PREP Act

Declaration.

Therefore, in accordance with Sections IV and VII of the PREP Act Declaration as well as the PREP Act (42 U.S.C. § 247d-6d), the Department of Defense contracting via assisted acquisition on behalf of the HHS, expressly acknowledges and agrees that the HHS Declaration cited above, specifically its language providing immunity from suit and liability is applicable to this acquisition as long as Contractors activities fall within the terms and conditions of the PREP Act and the PREP Act Declaration.

The Government may not use, or authorize the use of, any products or materials provided under this contract, unless such use occurs in the United States (or a U.S. territory where U.S. law applies such as embassies, military and NATO installations) and is protected from liability under a declaration issued under the PREP Act, or a successor COVID-19 PREP Act Declaration of equal or greater scope. Any use where the application of the PREP Act is in question will be discussed with Moderna prior to use and, if the parties disagree on such use, the dispute will be resolved according to the "Disputes Clause" (52.233-1)

The items and technology covered by this Contract are being developed for both civil and military applications.

H.9 [***].

H.10 Ensuring Sufficient Supply of the Product

1. In recognition of the Government's significant funding for the development and manufacturing of the product in this contract and the Government's need to provide sufficient quantities of a COVID-19 vaccine to protect the United States population, the Government shall have the remedy described in this section to ensure sufficient supply of the product to meet the needs of the public health or national security. This remedy is not available to the Government unless and until both of the following conditions ((a) and (b)) are met:

a. Moderna gives written notice, required to be submitted to the Government [***], of:

(i) any formal management decision to terminate manufacturing of this product vaccine prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons or;

(ii) any formal management decision to discontinue sale of this product vaccine to the Government prior to delivery of any doses to USG under this contract, including all exercised options, other than as a result of clinical failure, or serious technical or safety reasons; or

(iii) any filing that anticipates Federal bankruptcy protection; and

b. Moderna has submitted an Emergency Use Authorization application under §564 of the FD&C Act or a biologics license application provisions of §351(a) of the Public Health Service Act (PHSA).

2. If both conditions listed in section 1 occur, Moderna, upon the request of the Government, shall provide the following items necessary for the Government to pursue manufacturing of this product vaccine with a third party for exclusive sale to the U.S. Government:

a. a writing evidencing a non-exclusive, nontransferable, irrevocable (except for cause), royalty-free paid-up license to practice or have practiced for or on behalf of the U.S. Government any Moderna Background Patent, Copyright, other Moderna Intellectual Property, Moderna Know-How, Moderna Technical Data rights necessary to manufacture doses of the mRNA-1273 vaccine;

b. necessary FDA regulatory filings or authorizations owned or controlled by Moderna related to this product vaccine and any confirmatory instrument pertaining thereto; and

c. any outstanding Deliverables contemplated or materials purchased under this contract.

3. This remedy will remain available until the end of the contract.

H.11 [***].

H.12 Transportation to Final Destination

During the course of performance under this contract, the Government may require storage of the filled drug product (FDP) before delivery to the final government location. In these circumstances, the Government will accept FDP at the contractor facility (Origin). The contractor; however, shall continue to be responsible for secure delivery of the vaccine to its final destination as identified on this contract. [***].

H.13 Validation of IP/Data

The Parties acknowledge that background intellectual property and technical data assertions have been made and evaluated by the parties. The parties agree that, should additional information relevant to these assertions become available, the parties will reevaluate said assertions as necessary in the future.

H.14 Novation

Upon Moderna, US, Inc.'s registration in the System for Award Management, the Government will, at the Contractor's request, complete a novation of this Contract to recognize Moderna US, Inc. as a counterparty instead of Moderna TX, Inc. This novation will be completed through a modification executed by the Government that identifies Moderna US, Inc. as the contracting party for all purposes as if it had originally executed the Contract.

H.15 Base & Option 1 Delivery Acceleration

In an effort to accelerate production of the mRNA-1273 vaccine, [***] within the Option 1 period via a Modification to the contract.

If these manufacturing slots are successfully utilized, [***] above what was projected by Moderna and assumed within the price per dose for the doses of mRNA-1273 vaccine delivered in the Base Period and Option 1. However, because the Government is funding the additional slots within the Base and Option 1 periods in order to accelerate production, the Government is entitled to an adjustment under the conditions outlined. The Government and Moderna agree to the following:

1. If the Government exercises Option 2 (NLT 15 May):

a. Moderna will reduce the cost of Option 2 by \$[***] for each successfully accelerated drug product fill under the Base Period ([***) and \$[***] for each successfully accelerated drug product fill under Option 1 ([***)).

2. If the Government does not exercise Option 2 (NLT 15 May):

a. In the event Moderna timely cancels the manufacturing slots and/or is able to otherwise fully utilize the slots originally reserved for production in the Option 2 period, Moderna agrees to credit the Government \$[***] for [***] and \$[***] for [***]. In no case shall the number of drug product manufacturing slots credited exceed the number of successfully accelerated drug product manufacturing fills under the Base Period and Option 1. It is understood that Moderna will make all good-faith efforts to fill reserved slots or cancel reservations in a timely manner (i.e. within the time period required by the subcontractor).

b. In the event that Moderna is unable to fill those reserved slots (i.e. due to lack of demand) and cancels slots, Moderna shall be entitled to recoup those reservation cancellation costs from the USG. The process is outlined as follows:

1.) Moderna shall submit documentation to the USG of the following:

- i.) Cancellation notice to the subcontractor,
- ii.) The basis of the cancellation, and
- iii.) Cancellation fees incurred.

2.) Moderna shall reduce credits to the USG under paragraph 2a) of this clause, IAW agreed cancellation costs incurred.

3.) Bi-lateral agreement of the final credit shall be included in a modification to the contract. Net credit shall be deducted from final payments under the contract.

H.16 Delivery Schedule, as revised 11Feb2021 via modification P00004

[***].

H.17 Post-Termination Disposition of Undelivered Product

For the avoidance of doubt, if the USG elects to terminate the exercised CLINs prior to acceptance and delivery in full of the required quantities of mRNA-1273, Moderna will be free to direct any unaccepted/undelivered supplies of mRNA-1273 to customers other than the USG, at its discretion, without further obligation of either party with regard to such unaccepted/undelivered supplies of mRNA-1273. The contract will be bilaterally modified to decrease the quantities by the agreed upon volume.

H.18 [*]**

In order to facilitate projections and invoicing, the Government shall provide or direct a third party ([**]) to provide to Moderna (1) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; (2) actual quantities of Moderna [**] with 8.0mL vials during the reporting period; and (3) the number of [**] remaining in inventory and available for upcoming shipments. This information will be provided to Moderna at a frequency of at least twice monthly.

For each 8.0mL fill volume (1600mcg) vial of vaccine shipped with a [**].

Both parties acknowledge that the delivery schedule is based on an [**] 8.0mL fill volume (1600mcg) vial delivered. In accordance with the agreed approach for invoicing and counting doses toward Moderna's delivery requirement, [**]. Specifically for purposes of adhering to the scheduled delivery dates set forth in this contract for the Base Period, Option 1 and Option 2, schedule shall be deemed to have been met once doses are released by Moderna and are available for order.

H.19 Product [] (as added via P00018)**

Specific to CLINs 3001 and 4001, Moderna will deliver to the Government [**]:

- a. Adult Primary Series (mRNA-1273 or other, as determined by EUA/BLA and any related supplement or amendment thereto accepted and authorized/licensed by FDA and mutually agreed upon; [**])
- b. [**]
- c. [**]

For avoidance of doubt, all doses delivered to the Government must be suitable for use in the United States pursuant to an active EUA or approved BLA at the time of product delivery. [**].

If US regulatory authorities determine there is a need for an updated vaccine containing one or more variant mRNA sequences for any reason, including improved efficacy against new or emerging virus strains, the Parties agree to work together in good faith to discuss any such situation and any potential impact on this contract. [**].

Both parties acknowledge that the EUA for mRNA-1273 may be expanded such that doses procured under this contract may have utility beyond the currently authorized indications/populations, and in the event of any such expansion, the Government will not be restricted hereunder from use of mRNA-1273 in accordance with the full scope of any FDA authorization and CDC recommendation to the extent consistent with the Government's obligations under Section H.8 and the terms of Section H.20.

The Government and Moderna agree that the total monthly delivery quantities for CLIN 3001 and 4001 will follow the following Delivery Schedule:

[**]

The Government and Moderna agree as follows:

- [**].
- *Sale of doses to the African Union.* The Government is agreeing to defer delivery of 33,000,000 doses previously scheduled for delivery in December and February to facilitate Moderna's supply of 50,000,000 doses of mRNA-1273 to the African Union (AU) at a not-for-profit price.
- [**].

EUA Wind Down. It is anticipated that all mRNA-1273 under this contract will be delivered in accordance with an active EUA. If a BLA is issued during the term of this Contract for the mRNA-1273 vaccine, the Government and Moderna shall discuss an appropriate transition of mRNA-1273 to BLA which will include that any doses subsequently provided to the Government under this Contract are appropriately labeled and are otherwise suitable for use in the United States under the terms of the EUA (before expiration) or the BLA.

H.20 Donation of Excess Product

a. If the Government determines that a quantity of doses of mRNA-1273 supplied to the Government under this contract is no longer needed by the Government, the Government may donate such doses to a foreign nation or nongovernmental organization (NGO) facilitating donation to a foreign nation, subject to the remainder of this Clause H.20. The Government shall notify Contractor in writing prior to any proposed donation to a foreign nation or NGO, which notice will include [***].

b. Contractor must verify in writing that all of the required conditions below are met before any such donation is made, [***]:

(i) [***];

(ii) [***];

(iii) [***]; and

(iv) [***].

c. Additionally, the Government may donate product for use in the clinical study to be conducted pursuant to the Clinical Trial Agreement (as amended on October 28, 2021) between The National Institute of Allergy and Infectious Disease (“NIAID”) and the South African Medical Research Counsel (“SAMRC”) under Protocol CoVPN 3008 (the “CoVPN 3008 Study”), subject to the Government’s having a binding written agreement(s) in place with the sponsor that satisfies the conditions set forth below in this clause (c):

- (i) [***],
- (ii) [***];
- (iii) [***].
- (iv) [***];
- (v) [***];
- (vi) [***];
- (vii) [***];
- (viii) [***];
- (ix) [***]; and
- (x) [***].

d. The Government's donations will be from supplies of vaccine delivered to and accepted by the Government. To the extent the Government commits to deliver doses that have not yet been physically delivered to the Government, such donation will not occur until such doses have been delivered to the Government. The Government will be responsible for delivery of the donated doses to, and coordination of delivery with, the receiving foreign nation, clinical study sponsor, or NGO, as applicable. The Government or the receiving foreign nation, clinical study sponsor, or NGO, as applicable, will (i) satisfy all customs shipping requirements for import and export of the product; and (ii) as the exporter, file any required FDA export notifications. To the extent not already provided to the Government, the Contractor will provide all information necessary to complete any requirements identified in this paragraph in advance of shipment.

e. When the conditions above are met for any donation, the Parties [***].

f. [***].

g. Shipment of any donated doses under this Article does not constitute a violation of the Defense Production Act.

H.21 CDC Healthcare Provider List

To ensure timely communication is provided to health care providers, the USG has provided Moderna the mailing list for the Centers for Disease Control and Prevention (CDC) healthcare providers administering Moderna's vaccine and boosters in order for Moderna to send information regarding boosters that were authorized by the FDA on October 20, 2021. Moderna agrees to the terms below of the handling of the CDC Healthcare Provider List.

1. Moderna shall use the CDC Healthcare Provider List only for the express purpose of the specific mailing regarding Moderna's FDA-authorized booster product/EUA expansion;
2. Moderna shall not share or provide this list to any outside parties other than those who are supporting this specific mailing; and
3. Moderna shall delete (and require any other parties to delete) the list once they have completed the mailing.

SECTION J - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

The following have been modified:

Document Type	Description	Page #	Date
Exhibit A	CDRLs	15	11 February 2021
Exhibit B	Donation of Excess Product	11	5 December 2021
Attachment 0001	Supply Chain Resiliency Plan for CDRL A010	3	23 July 2020
Attachment 0002	Security Plan	7	23 July 2020
Attachment 0003	Dose Tracking Template Draft Moderna	Excel	15 July 2020
Attachment 0004	Data Rights	3	7 August 2020
Attachment 0005	***]	2	7 August 2020
Attachment 0006	ModernaTx, Inc. Background Intellectual Property	3	6 August 2020
Attachment 0007	Performance Base Payment Milestone Schedule	1	14 June 2021
Attachment 0008	Performance Base Payment Milestone Billing Plan	16	3 September 2021
Attachment 0009	HRPAS Moderna Letter	1	3 September 2020

(End of Summary of Changes)

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE OF PAGES

1 13

2. AMENDMENT/MODIFICATION NO.

3. EFFECTIVE DATE

4. REQUISITION/PURCHASE REQ. NO.

5. PROJECT NO.(If applicable)

P00021

21-JAN-2022

See Schedule

6. ISSUED BY CODE

W58P05

7. ADMINISTERED BY (If other than item 6) CODE

S2206A

ACC-APG - COVID RESPONSE - W58P05
 6472 INTEGRITY COURT (BUILDING 4401)
 ABERDEEN PROVING GROUND MD 21005-3013

DCMA BOSTON
 495 SUMMER STREET
 BOSTON MA 02210-2138

8. NAME AND ADDRESS OF CONTRACTOR (No., Street, County, State and Zip Code)

9A. AMENDMENT OF SOLICITATION NO.

9B. DATED (SEE ITEM 11)

MODERNA US, INC.

[***]

200 TECHNOLOGY SQ

CAMBRIDGE MA 02139-3578

X

10A. MOD. OF CONTRACT/ORDER NO.

W911QY20C0100

X

10B. DATED (SEE ITEM 13)

CODE 8PTM0

FACILITY CODE

09-Aug-2020

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offer is extended, is not extended.

Offer must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended by one of the following methods:

(a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

See Schedule

**13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS.
IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.**

- A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
- B. THE ABOVE NUMBERED CONTRACT /ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(B).
- C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
- D. OTHER (Specify type of modification and authority)

X

E. IMPORTANT: Contractor is not, is required to sign this document and return 1 copies to the issuing office.**14. DESCRIPTION OF AMENDMENT /MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)**

Modification Control Number: [***]

See Block 14 Continuation Page

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)

Shaun Ryan, SVP & Deputy General Counsel

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)

[***]

TEL: [***] EMAIL: [***]

15B. CONTRACT OR/OFFEROR

15C. DATE SIGNED

16B. UNITED STATES OF AMERICA

16C. DATE SIGNED

/s/ Shaun Ryan

1/20/2022

BY [***]

21-JAN-2022

(Signature of person authorized to sign)

(Signature of Contracting Officer)

EXCEPTION TO SF 30
 APPROVED BY OIRM 11-84

30-105-04

STANDARD FORM 30 (Rev. 10-83)
 Prescribed by GSA
 FAR (48 CFR) 53.243

SECTION SF 30 BLOCK 14 CONTINUATION PAGE

SUMMARY OF CHANGES

SECTION SF 30 - BLOCK 14 CONTINUATION PAGE

The following have been added by full text:

P00021

OBLIGATION AMOUNT: \$203,142.00

a. The purpose of this modification (P00021) is to:

- Revise Statement of Work in sections C.3.4, C.3.5, and C.7 (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties)
- Extend and fund VMI Storage by six month from 1 January 2022 to 30 June 2022 on CLIN 0006 (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties)
- Update Exhibit B as outlined in clause H.20 with donation information for multiple recipients (Authority FAR 43.103(a)(3), Mutual Agreement of the Parties)

b. This modification was requested by the program office to meet the Government's mission requirements.

c. The total funded amount and total contract value amount increase by \$203,142.00 from \$8,145,591,662.60 to \$8,145,794,804.60.

All other terms and conditions remain unchanged.

SECTION A - SOLICITATION/CONTRACT FORM

The total cost of this contract was increased by \$203,142.00 from \$8,145,591,662.60 to \$8,145,794,804.60.

SECTION B - SUPPLIES OR SERVICES AND PRICES

CLIN 0006 is added as follows:

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
0006		6	Months	\$33,857.00	\$203,142.00

Vendor Managed Inventory Extentions FFP

a. The contractor shall secure, manage and maintain storage for up to 100M doses of mRNA-1273 vaccine and deliver to the designated government facility in accordance with Section F.

FOB: Destination

PURCHASE REQUEST NUMBER: 0011737324

PSC CD: 6505

NET AMT \$203,142.00

ACRN AP \$203,142.00

CIN: GFEB001173732400001

SECTION C - DESCRIPTIONS AND SPECIFICATIONS

The following have been modified:

STATEMENT OF WORK LARGE SCALE PRODUCTION OF SARS-CoV-2 VACCINE

C.1 **SCOPE.** The Department of Defense and Health and Human Services (HHS) require large scale manufacturing of vaccine doses in support of the national emergency response to the Coronavirus Disease 2019 (COVID-19) for the United States Government (USG) and the US population.

C.1.1 **Background.** In December 2019, a novel coronavirus now known as SARS-CoV-2 was first detected in Wuhan, Hubei Province, People's Republic of China, causing outbreaks of the coronavirus disease COVID-19 that has now spread globally. The Secretary of Health and Human Service declared a public health emergency on January 31, 2020, under section 319 of the Public Health Service Act (42 U.S.C. 247d), in response to COVID-19. On March 1, 2020, the President of the United States, pursuant to sections 01 and 301 of the National Emergencies Act (50 U.S.C. 1601 et seq.) and consistent with section 1135 of the Social Security Act (SSA), as amended (42 U.S.C. 1320b-5), proclaimed that the COVID-19 outbreak in the United States constitutes a national emergency.

C.1.1.1 Under Operation Warp Speed (OWS), the Department of Defense and HHS are leading a whole of nation effort to ensure development of promising vaccine, diagnostic and therapeutic candidates and ensure that these medical countermeasures are available in the quantities required to reduce SARS-CoV-2 transmission, identify prior and/or current infection, and improve patient care, thereby mitigating the impact of COVID-19 on the nation and its people. The DoD Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO-CBRD) is providing expertise and contracting support to HHS, in compliance with PL 115-92 Authorization Letter for DoD Medical Priorities, through an Interagency Agreement, signed April 23, 2020. As OWS products progress to clinical trials to evaluate the safety and efficacy of vaccines and therapeutics, it is critical that, in parallel, the USG supports large scale manufacturing so that vaccine doses or therapeutic treatment courses are immediately available for nationwide access as soon as a positive efficacy signal is obtained and the medical countermeasures are authorized for widespread use.

C.1.2 **Objective:** The objective of this effort is to obtain the following:

- a. Base Period: Large scale manufacturing of 100 million vaccine doses
- b. Option Period 1: Large scale manufacturing of 100 million vaccine doses
- c. Option Period 2: Large scale manufacturing of 100 million vaccine doses
- d. Option Period 3: Large scale manufacturing of 100 million vaccine doses
- e. Option Period 4: Large scale manufacturing of 100 million vaccine doses

The Base Period is 9 months, with overlapping options for a total of 20 months if all options are exercised.

C.1.3 Consistent with the Updated EUA Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) dated 01 April 2021, up to 15 doses may be extracted from Moderna's newly authorized multidose vials with 8.0mL fill volume (1600mcg). The Government and Moderna agree that 15 doses per vial are only attainable using premium low dead volume (LDV) syringes, which are in short supply globally. Utilizing initial ancillary equipment, vaccine administration personnel can reliably extract 13 doses from these vials; however, the Government has identified needle/syringe combinations that can be used to extract 14 doses.

C.1.3.1 Given the two parties' shared interest in reducing vaccine waste and accelerating the availability of Moderna's SARS-CoV-2 vaccine doses, the Government and Moderna intend that the Moderna vaccines doses be administered with needles and syringes compatible with extraction of 14 doses when possible. Toward this end, the Government shall maintain a list of syringe and/or needle combinations which will allow extraction of 14 doses per 8.0mL vial, which list shall be updated jointly by the Government and Moderna as any additional syringe and/or needle combinations compatible with extraction of 14 doses/vial are identified. Furthermore, the Government will, to the extent that appropriate needles and syringes are available, assemble and ship kits containing sufficient quantities of syringes and needles compatible with extraction of 14 doses per vial (Kit Moderna 140) with Moderna's SARS-CoV-2 vaccine. The Government expects that these kits will be available beginning 01 May 2021 for a significant portion of Moderna's remaining deliveries. If, however, appropriate syringes and needles are not available, the Government will revert to shipping the Kit Moderna 130 with Moderna's SARS-CoV-2 vaccine.

C.2 APPLICABLE DOCUMENTS.

C.2.1 Federal Documents:

C.2.1.1 Title 21 Code of Federal Regulations (CFR), Food and Drugs: Part 210, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; and, Part 211, Current Good Manufacturing Practice In Manufacturing, Processing, Packing, or Holding of Drugs; General. (https://www.ecfr.gov/cgi-bin/text-idx?SID=a95cab20f443897a400bb7e44a27cf4c&mc=true&tpl=/ecfrbrowse/Title21/21cfrv4_02.tpl#0)

C.3 **REQUIREMENTS.** Independently, and not as an agent of the USG, in accordance with the Proposal submitted by Moderna US, Inc. in response to Solicitation Number W911QY20R0043, Titled, "Advanced Procurement of mRNA-1273 Vaccine for Prevention of SARS-CoV-2 Coronavirus (COVID-19)", dated July 10, 2020 (and any subsequent USG-approved revisions thereto), the contractor shall provide all necessary services, qualified personnel, material, equipment and facilities (not otherwise provided by the USG under the terms of this contract) to perform the specific tasks set forth below.

C.3.1 Contract Line Item Number (CLIN) 0001 - Base Period: Large Scale Manufacturing of 100 Million Vaccine Doses.

C.3.1.1 The contractor shall complete all scope required for the production, release and delivery use of 100 million Final Drug Product (FDP) doses of a SARS-CoV-2 mRNA-1273 vaccine. This shall include, the following tasks and other activities reasonably contemplated by such task:

C.3.1.1.1 Storage of FDP doses prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. Storage and maintenance of the vaccine prior to delivery shall be under conditions and at temperatures necessary to retain stability for use as prescribed in this contract for a period of 12 months. (Based on FDP stability data that supports a 12-month shelf-life, subject to FDA confirmation of the assigned shelf-life.) Ensure requirements of 21CFR207, Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution are met prior to distribution to the CDC. Documents shall be provided under CDRL A002, FDA Interactions and Inspections Documentation.

C.3.1.1.2 cGMP manufacturing of 100 million doses fully compliant with 21 CFR 210 and 211.

C.3.1.1.3 Ensuring that vial labeling and packaging is consistent with FDA guidance for use in target populations and that labeling is updated as appropriate.

C.3.1.1.4 Coordinating with FDA to establish an approved commercial vial label, carton and packaging insert (printed or electronic).

C.3.1.1.5 Ensuring the product complies with the Drug Supply Chain Security Act (DSCSA), Sections 581-585 of PL 113-54 (Nov. 27, 2013), including product verification, serialization, traceability and detection and response requirements, subject to any exceptions established by or the enforcement discretion of the FDA, including "Exemption from Certain Product Tracing and Product Identification Requirements Under Section 582 of the FD&C Act" (April 2020).

C.3.1.1.6 In coordination with the USG, the contractor shall conduct a demonstration of the vaccine shipping process prior to the first delivery of FDP doses at a time mutually agreed to by the contractor and the USG. Moderna shall provide specifications and details associated with the shipping process and containers (IAW CDRL A005) to enable the USG to adequately plan and prepare for potential distribution of the vaccine.

C.3.1.1.7 Following release of product the contractor shall, promptly deliver product to the designated delivery site via a qualified distribution vendor in accordance with Section F and paragraph C.7 below. In the unforeseen event that a designated delivery site cannot receive product and the contractor provides storage beyond 20 days of product release, the contract will be subject to modification for acceptance purposes.

C.3.1.2 Site Visits and Audits. The contractor shall accommodate periodic or ad hoc site visits by BARDA and FDA representatives for required site visits and audits at facilities used to support this contract throughout the period of performance of the contract.

C.3.1.2.1 BARDA Audits. If issues are identified during an audit, the contractor shall submit a report detailing the finding and corrective action(s) in accordance with CDRL A001.

C.3.1.2.2 FDA Audits. The Contractor shall notify the Contracting Officer and Contracting Officer's Representative (COR) within [***] of a scheduled FDA audit or within [***] of an ad hoc site visit or audit if the FDA does not provide advance notice. The contractor shall provide copies of any FDA Audit Report received from subcontractors that occur as a result of this contract or for this product within [***] of receiving correspondence from the FDA or third party in accordance with CDRL A002. The Contractor shall provide the Contracting Officer with a plan for addressing areas of nonconformance, if any are identified, within [***] of submittal of the audit report in accordance with CDRL A002.

C.3.1.2.3 FDA Interactions. The contractor shall provide copies of the plan and processes that will ensure the USG has visibility and input on all FDA communications regarding the drugs and biologics for the following, but not limited to: FDA interactions, FDA meetings, communications, submissions, inspections, and enforcement documentation in accordance with CDRL A002.

C.3.2 **CLIN 1001 - Option Period 1: Large Scale Manufacturing of 100 Million Vaccine Doses.**

C.3.2.1 The contractor shall complete all scope required for the production, release and delivery use of 100 million FDP doses of a SARS-CoV-2 mRNA-1273 vaccine. This shall include the following tasks and other activities reasonably contemplated by such tasks:

C.3.2.1.1 Storage of FDP doses prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. Storage and maintenance of the vaccine prior to delivery shall be under conditions and at temperatures necessary to retain stability for use as prescribed in this contract for a period of 12 months. (Based on FDP stability data that supports a 12-month shelf-life, subject to FDA confirmation of the assigned shelf-life.) Ensure requirements of 21CFR207, Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution are met prior to distribution to the CDC. Documents shall be provided under CDRL A002, FDA Interactions and Inspections Documentation.

C.3.2.1.2 cGMP manufacturing of 100 million doses, subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.2.1.3 Ensuring that vial labeling and packaging is consistent with FDA guidance for use in target populations and that labeling is updated.

C.3.2.1.4 Ensuring the product complies with the Drug Supply Chain Security Act (DSCSA), Sections 581-585 of PL 113-54 (Nov. 27, 2013), including product verification, serialization, traceability and detection and response requirements subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.2.1.5 Following release of the product the contractor shall deliver the product to the designated distribution site via a qualified distribution vendor in accordance with Section F and paragraph C.7 below. To the extent a natural disaster or other emergency affecting a designated delivery site restricts such site's ability to receive product, the Contractor and the USG will promptly agree on an alternate USG delivery location, or storage as Vendor Managed Inventory (VMI) at the contractor site.

C.3.2.2 Site Visits and Audits. The contractor shall accommodate periodic or ad hoc site visits by BARDA and FDA representatives for required site visits and audits at facilities used to support this contract throughout the period of performance of the contract.

C.3.2.2.1 BARDA Audits. If issues are identified during an audit, the contractor shall submit a report detailing the finding and corrective action(s) in accordance with CDRL A001.

C.3.2.2.2 FDA Audits. The Contractor shall notify the Contracting Officer and COR within [***] of a scheduled FDA audit or within [***] of an ad hoc site visit or audit if the FDA does not provide advance notice. The contractor shall provide copies of any FDA Audit Report received from subcontractors that occur as a result of this contract or for this product within [***] of receiving correspondence from the FDA or third party in accordance with CDRL A015. The Contractor shall provide the Contracting Officer with a plan for addressing areas of nonconformance, if any are identified, within [***] of submittal of the audit report in accordance with CDRL A002.

C.3.2.2.3 FDA Interactions. The contractor shall provide copies of the plan and processes that will ensure the USG has visibility and input on all FDA communications regarding the drugs and biologics for the following, but not limited to: FDA interactions, FDA meetings, communications, submissions, inspections, and enforcement documentation in accordance with CDRL A002.

C.3.3 **CLIN 2001 - Option Period 2: Large Scale Manufacturing of 100 Million Vaccine Doses.**

C.3.3.1 The contractor shall complete all scope required for the production, release and delivery use of 100 million FDP doses of a SARS-CoV-2 mRNA-1273 vaccine. This shall include the following tasks and other activities reasonably contemplated by such tasks:

C.3.3.1.1 Storage of FDP doses prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. Storage and maintenance of the vaccine prior to delivery shall be under conditions and at temperatures necessary to retain stability for use as prescribed in this contract for a period of 12 months. (Based on FDP stability data that supports a 12-month shelf-life, subject to FDA confirmation of the assigned shelf-life.) Ensure requirements of 21CFR207, Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution are met prior to distribution to the CDC. Documents shall be provided under CDRL A002, FDA Interactions and Inspections Documentation.

C.3.3.1.2 cGMP manufacturing of 100 million doses, subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.3.1.3 Ensuring that vial labeling and packaging is consistent with FDA guidance for use in target populations and that labeling is updated as appropriate.

C.3.3.1.4 Ensuring that the product complies with the Drug Supply Chain Security Act (DSCSA), Sections 581- 585 of PL 113-54 (Nov. 27, 2013), including product verification, serialization, traceability and detection and response requirements, subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.3.1.5 Following release the contractor shall deliver product to the nearest designated distribution site via a qualified distribution vendor in accordance with Section F and paragraph C.7 below. To the extent a natural disaster or other emergency affecting a designated delivery site restricts such site's ability to receive product, the Contractor and the USG will promptly agree on an alternate USG delivery location, or storage as Vendor Managed Inventory (VMI) at the contractor site.

C.3.3.2 Site Visits and Audits. The contractor shall accommodate periodic or ad hoc site visits by BARDA and FDA representatives for required site visits and audits at facilities used to support this contract throughout the period of performance of the contract.

C.3.3.2.1 BARDA Audits. If issues are identified during an audit, the contractor shall submit a report detailing the finding and corrective action(s) in accordance with CDRL A001.

C.3.3.2.2 FDA Audits. The Contractor shall notify the Contracting Officer and COR within [***] of a scheduled FDA audit or within [***] of an ad hoc site visit or audit if the FDA does not provide advance notice. The contractor shall provide copies of any FDA Audit Report received from subcontractors that occur as a result of this contract or for this product within [***] of receiving correspondence from the FDA or third party in accordance with CDRL A002. The Contractor shall provide the Contracting Officer with a plan for addressing areas of nonconformance, if any are identified, within [***] of submittal of the audit report in accordance with CDRL A002.

C.3.3.2.3 FDA Interactions. The contractor shall provide copies of the plan and processes that will ensure the USG has visibility and input on all FDA communications regarding the drugs and biologics for the following, but not limited to: FDA interactions, FDA meetings, communications, submissions, inspections, and enforcement documentation in accordance with CDRL A002.

C.3.4 CLIN 3001 - Option Period 3: Large Scale Manufacturing of 100 Million Vaccine Doses.

C.3.4.1 The contractor shall complete all scope required for the production, release and delivery use of 100 million FDP doses of a SARS-CoV-2 mRNA-1273 vaccine. This shall include the following tasks and other activities reasonably contemplated by such tasks:

C.3.4.1.1 Storage of FDP doses prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. Storage and maintenance of the vaccine prior to delivery shall be under conditions and at temperatures necessary to retain stability for use as prescribed in this contract per C.7. (Based on FDP stability data that supports a 12-month shelf-life, subject to FDA confirmation of the assigned shelf- life.) Ensure requirements of 21CFR207, Registration of Producers of Drugs and Listing of Drugs in Commercial

Distribution are met prior to distribution to the CDC. Documents shall be provided under CDRL A002, FDA Interactions and Inspections Documentation.

C.3.4.1.2 cGMP manufacturing of 100 million doses, subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.4.1.3 Ensuring that vial labeling and packaging is consistent with FDA guidance for use in target populations and that labeling is updated.

C.3.4.1.4 Ensuring the product complies with the Drug Supply Chain Security Act (DSCSA), Sections 581-585 of PL 113-54 (Nov. 27, 2013), including product verification, serialization, traceability and detection and response requirements subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.4.1.5 Following release of the product the contractor shall deliver the product to the designated distribution site via a qualified distribution vendor in accordance with Section F and paragraph C.7 below. To the extent a natural disaster or other emergency affecting a designated delivery site restricts such site's ability to receive product, the Contractor and the USG will promptly agree on an alternate USG delivery location, or storage as Vendor Managed Inventory (VMI) at the contractor site.

C.3.4.2 Site Visits and Audits. The contractor shall accommodate periodic or ad hoc site visits by BARDA and FDA representatives for required site visits and audits at facilities used to support this contract throughout the period of performance of the contract.

C.3.4.2.1 BARDA Audits. If issues are identified during an audit, the contractor shall submit a report detailing the finding and corrective action(s) in accordance with CDRL A001.

C.3.4.2.2 FDA Audits. The Contractor shall notify the Contracting Officer and COR within [***] of a scheduled FDA audit or within [***] of an ad hoc site visit or audit if the FDA does not provide advance notice. The contractor shall provide copies of any FDA Audit Report received from subcontractors that occur as a result of this contract or for this product within [***] of receiving correspondence from the FDA or third party in accordance with CDRL A015. The Contractor shall provide the Contracting Officer with a plan for addressing areas of nonconformance, if any are identified, within [***] of submittal of the audit report in accordance with CDRL A002.

C.3.4.2.3 FDA Interactions. The contractor shall provide copies of the plan and processes that will ensure the USG has visibility and input on all FDA communications regarding mRNA-1273 for the following, but not limited to: FDA interactions, FDA meetings, communications, submissions, inspections, and enforcement documentation in accordance with CDRL A002.

C.3.5 CLIN 4001 - Option Period 4: Large Scale Manufacturing of 100 Million Vaccine Doses.

C.3.5.1 The contractor shall complete all scope required for the production, release and delivery use of 100 million FDP doses of a SARS-CoV-2 mRNA-1273 vaccine. This shall include the following tasks and other activities reasonably contemplated by such tasks:

C.3.5.1.1 Storage of FDP doses prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. Storage and maintenance of the vaccine prior to delivery shall be under conditions and at temperatures necessary to retain stability for use as prescribed in this contract per C.7. (Based on FDP stability data that supports a 12-month shelf-life, subject to FDA confirmation of the assigned shelf- life.) Ensure requirements of 21CFR207, Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution are met prior to distribution to the CDC. Documents shall be provided under CDRL A002, FDA Interactions and Inspections Documentation.

C.3.5.1.2 cGMP manufacturing of 100 million doses, subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.5.1.3 Ensuring that vial labeling and packaging is consistent with FDA guidance for use in target populations and that labeling is updated.

C.3.5.1.4 Ensuring the product complies with the Drug Supply Chain Security Act (DSCSA), Sections 581-585 of PL 113-54 (Nov. 27, 2013), including product verification, serialization, traceability and detection and response requirements subject to any exceptions established by or the enforcement discretion of the FDA.

C.3.5.1.5 Following release of the product the contractor shall deliver the product to the designated distribution site via a qualified distribution vendor in accordance with Section F and paragraph C.7 below. To the extent a natural disaster or other emergency affecting a designated delivery site restricts such site's ability to receive product, the Contractor and the USG will promptly agree on an alternate USG delivery location, or storage as Vendor Managed Inventory (VMI) at the contractor site.

C.3.5.2 Site Visits and Audits. The contractor shall accommodate periodic or ad hoc site visits by BARDA and FDA representatives for required site visits and audits at facilities used to support this contract throughout the period of performance of the contract.

C.3.5.2.1 BARDA Audits. If issues are identified during an audit, the contractor shall submit a report detailing the finding and corrective action(s) in accordance with CDRL A001.

C.3.5.2.2 FDA Audits. The Contractor shall notify the Contracting Officer and COR within [***] of a scheduled FDA audit or within [***] of an ad hoc site visit or audit if the FDA does not provide advance notice. The contractor shall provide copies of any FDA Audit Report received from subcontractors that occur as a result of this contract or for this product within [***] of receiving correspondence from the FDA or third party in accordance with CDRL A015. The Contractor shall provide the Contracting Officer with a plan for addressing areas of nonconformance, if any are identified, within [***] of submittal of the audit report in accordance with CDRL A002.

C.3.5.2.3 FDA Interactions. The contractor shall provide copies of the plan and processes that will ensure the USG has visibility and input on all FDA communications regarding the drugs and biologics for the following, but not limited to: FDA interactions, FDA meetings, communications, submissions, inspections, and enforcement documentation in accordance with CDRL A002.

C.4 **CLIN 0002: Data Deliverables**. The contractor shall provide the following in accordance with the Contract Data Requirements List (CDRL), DD Forms 1423, provided at Appendix A.

C.4.1 Monthly Inventory Report (CDRL A003), detailing at a minimum, raw materials, formulated LNPs, and the fill, finish, and released product.

C.4.2 Quality Management Plan. The contractor shall provide a Quality Management Plan, in accordance with CDRL A004, describing the quality policy and objectives, management review, competencies and training, process document control, feedback, evaluation, corrective action and preventive action, process improvement, measurement, and data analysis processes. The framework is normally divided into infrastructure, senior management responsibility, resource management, lifecycle management, and quality management system evaluation.

C.4.3 Shipping Documentation (CDRL A005) for all Finished Drug Product (FDP) transferring from the contractor's fill/finish facility to a USG facility. The contractor shall obtain concurrence on planned shipment protocols prior to transport.

C.4.4 Expiring Items Report (CDRL A006) for all FDP in the USG's possession.

C.4.5 Key Personnel Listing (CDRL A007).

C.4.6 Monthly Technical Progress Report (CDRL A008), to include an Integrated Master Schedule, identifying key activities and contract status.

C.4.7 Final Technical Report (CDRL A009), documenting the work performed and results obtained for the entire contract period of performance.

C.4.8 Supply Chain Resiliency Plan (SCRCP). The contractor shall provide, in accordance with CDRL A010 and CDRL Attachment 0001, a comprehensive SCRCP that provides for identification and reporting of critical components associated with the secure supply of drug substance, drug product, and work-in-process through to finished goods, and key equipment suppliers and their locations, including addresses, points of contact, and work performed per location, to include subcontractors.

C.4.9 Risk Management Plan (RMP). The Contractor shall provide an RMP in accordance with CDRL A011 that outlines the impacts of each risk in relation to the cost, schedule, and performance objectives. The plan shall include risk mitigation strategies. Each risk mitigation strategy shall capture how the corrective action will reduce impacts on cost, schedule and performance. The following RMP information shall be included in the Monthly Technical Progress Report (CDRL A008).

Risk Register content:

- a. Manuf/FF -risks or possible delays. If none N/A
- b. Supply chain – same as above
- c. Distribution challenges – same as above
- d. Regulatory – same as above

C.4.10 Manufacturing Reports and Dose Tracking. The Contractor shall provide, in accordance with CDRL A013, manufacturing reports and manufacturing dose tracking projections and actuals utilizing the USG-provided “COVID-19 Dose Tracking Template” (CDRL Attachment 0003).

C.4.11 Product Acceptance Report (for each lot of Drug Product). The contractor shall provide, in accordance with CDRL A014, pictures of the drug product with lot number, drug product lot tree, list of associated deviations (from drug substance and product), and a Certificate of Analysis.

C.4.12 Incident Report. The contractor shall communicate to BARDA and document all critical programmatic concerns, issues, or probable risks that have or are likely to significantly impact project schedule and/or cost and/or performance in accordance with CDRL A016. “Significant” is frequently defined as a 10% or greater cost or schedule variance within a control account, but should be confirmed in consultation with the COR. Incidents that present liability to the project even without cost/schedule impact, such as breach of GCP during a clinical study, shall also be reported.

C.4.13 FDA Correspondence. The contractor shall provide any correspondence between Contractor and FDA relevant to the scope of this contract and submit in accordance with CDRL A017.

C.4.14 Press Releases. The contractor shall accurately and factually represent the work conducted under this contract in all press releases. The contractor shall provide an advance copy of any press release in accordance with CDRL A018.

C.4.15 Manufacturing Development Plan. The contractor shall provide a Manufacturing Development Plan, in accordance with CDRL A025, describing the manufacturing process for the drug/biologic product to ensure conformity with §501(a)(2)(B) of the Food, Drug, and Cosmetics Act (FD&C Act, Title 21 United States Code (USC) §351 (a)(2)(B)), regarding good manufacturing practices (GMP).

C.5 Administration.

C.5.1 Post Award Teleconference. The contractor shall host a Post Award Teleconference within 15 calendar days after contract award.

C.5.1.1 The contractor shall provide an Agenda, IAW CDRL A020, detailing the planned activities for the subsequent 30 calendar days and shall discuss agenda items for the Post Award Kickoff Meeting.

C.5.1.2 The contractor shall provide Meeting Minutes IAW CDRL A021.

C.5.2 **Post Award Kickoff Meeting.** The contracting officer may request the contractor host a contract Kick-Off Meeting within 30 calendar days after contract award via teleconference. The contracting officer shall establish the date and time of the conference and prepare the agenda to include discussion on contract activities and schedule.

C.5.3 **Bi-Weekly Teleconference.** The contractor shall participate in bi-weekly teleconferences (or more frequent meetings required by the USG if warranted based on contract activities) to discuss performance on the contract.

C.5.4 The contractor shall provide an Agenda, IAW CDRL A020; Meeting Minutes in accordance with CDRL A021; and, Presentation Material in accordance with CDRL A022 for each of the aforementioned teleconferences or meetings throughout the contract period of performance.

C.5.5 **Daily "Check-In".** The contractor shall participate in a daily "check-in" (via teleconference or email) to address key cost, schedule and technical updates. Daily updates may be shared with senior USG leaders during the COVID- 19 response and should be provided on a non-confidential basis, unless the update includes confidential information in which case, the contractor shall provide the update in both confidential and non-confidential formats. Daily check-ins may occur on weekdays, excluding federal holidays. Upon request of the USG, check-ins may also occur on weekends and on federal holidays, provided at least 24 hours' notice.

C.6 **Security.**

C.6.1 **Access and General Protection/Security Policy and Procedures.** The contractor shall provide all information required for background checks necessary to access critical information related to OWS, and to meet USG installation access requirements to be accomplished by the installation Director of Emergency Services or Security Office. The contractor employees shall comply with all personnel identity verification requirements as directed by the USG and/or local policy. In addition to the changes otherwise authorized by the changes clause of this contract, should the security status of OWS change the USG may require changes in the contractor's security matters or processes. In addition to the industry standards for employment background checks, the contractor shall be willing to have key individuals, in exceptionally sensitive positions, identified for additional vetting by the United States USG.

C.6.2 **Security Program and Plan.** The contractor shall implement a comprehensive security program that provides overall protection of personnel, information, data, and facilities associated with fulfilling the USG's requirement. The contractor's security practices and procedures shall be detailed in a Security Plan, in accordance with CDRL A019, and shall demonstrate how the contractor shall meet and adhere to the security requirements outlined in CDRL Attachment 0002. This plan shall be delivered to the USG within 45 days of award, and the USG will review in detail and submit comments within ten (10) business days to the Contracting Officer (CO) to be forwarded to the Contractor. The Contractor shall review the Security Plan comments, and, submit a final Security Plan to the U.S. USG within thirty (30) calendar days after receipt of the comments. The Security Plan shall include a timeline for compliance of all the required security measures outlined in CDRL Attachment 0002.

C.6.3 **Operational Security (OPSEC).** The contractor shall develop and submit an OPSEC Standard Operating Procedure (SOP)/Plan IAW CDRL A024. The contractor shall identify in the SOP/Plan critical information related to this contract, why it needs to be protected, where it is located, who is responsible for it, and how to protect it.

C.7 **Vendor Managed Inventory (VMI).** The Contractor shall provide the capability to store up to 100M doses of mRNA-1273 vaccine until 30 June 2022, in support of the extension of the delivery schedule for option 3 and 4. The contractor shall, in accordance with paragraph C.3.1.1.6, ensure the product storage of FDP doses for up to 12 months, in accordance with product labeling, and prior to delivery consistent with all FDA requirements to ensure that the product remains available for use in target populations. [***]. The contractor shall store the product to insure product quality with audible alarms and contacting. The contractor shall notify the USG within [***] of detection of an incident with the potential to impact product quality, and implement corrective actions to mitigate the incident. BARDA/JPEO-CBRND personnel may conduct Quality Audits of the storage facility, when deemed necessary. The contractor shall notify the USG of Corrective/Preventive actions within [***] of detection of an incident with potential to impacts product quality.

C.7.1 The USG will provide the contractor advance notice of the required delivery locations for the vaccine. The contractor shall ship mRNA-1273 vaccines to designated locations [***] in the United States. The contractor shall be responsible for shipment of all vaccine product whether acceptance is conducted at origin or destination. [***].

C.7.2 The vaccine product shall be shipped and tracked by the distribution vendor's shipping tracking number, to the USG-designated sites within the continental United States.

C.7.3 [***]. Implementation of a Vendor Managed Inventory Plan/SOP (CDRL A012) shall be provided to the USG. [***]. Notwithstanding either of the foregoing sentences, the contractor shall not be liable for loss of or damage to supplies caused by the negligence of officers, agents, or employees of the USG acting within the scope of their employment.

SECTION E - INSPECTION AND ACCEPTANCE

The following Acceptance/Inspection Schedule was added for CLIN 0006:

INSPECT AT	INSPECT BY	ACCEPT AT	ACCEPT BY
Destination	Government	Destination	Government

SECTION F - DELIVERIES OR PERFORMANCE

The following Delivery Schedule for CLIN 0006 has been added:

DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC / CAGE
30-JUN-2022	6	N/A FOB: Destination	

SECTION G - CONTRACT ADMINISTRATION DATA

Accounting and Appropriation

Summary for the Payment Office

As a result of this modification, the total funded amount for this document was increased by \$203,142.00 from \$8,145,591,662.60 to \$8,145,794,804.60.

CLIN 0006:

Funding on CLIN 0006 is initiated as follows:

ACRN: AP

CIN: GFEBS001173732400001

Acctng Data: 0212021202220400000665654260 S.0074658.5.44 6100.0152021001

Increase: \$203,142.00

Total: \$203,142.00

Cost Code: A5XAH

SECTION J - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACHMENTS

The following have been modified:

Document Type	Description	Page #	Date
Exhibit A	CDRLs	15	11 February 2021
Exhibit B	Donation of Excess Product	10	19 January 2022
Attachment 0001	Supply Chain Resiliency Plan for CDRL A010	3	23 July 2020
Attachment 0002	Security Plan	7	23 July 2020
Attachment 0003	Dose Tracking Template Draft Moderna	Excel	15 July 2020
Attachment 0004	Data Rights	3	7 August 2020
Attachment 0005	[***]	2	7 August 2020
Attachment 0006	ModernaTx, Inc. Background Intellectual Property	3	6 August 2020
Attachment 0007	Performance Base Payment Milestone Schedule	1	14 June 2021
Attachment 0008	Performance Base Payment Milestone Billing Plan	16	3 September 2021
Attachment 0009	HRPAS Moderna Letter	1	3 September 2020

(End of Summary of Changes)

SUBSIDIARIES

Subsidiary	Jurisdiction of Incorporation
Brizo Ltd.	Bermuda
Moderna Australia Pty Ltd	Australia
Moderna Austria GmbH	Austria
Moderna Biopharma Canada Corporation	Canada
Moderna Biotech Ireland Limited	Ireland
Moderna Biotech Securities, Inc.	Massachusetts
Moderna Biotech Spain, S.L.U.	Spain
Moderna Biotech UK Limited	United Kingdom
Moderna Charitable Foundation, Inc.	Delaware
Moderna France	France
Moderna Germany GmbH	Germany
Moderna Italy S.r.l.	Italy
Moderna Japan Co., Ltd.	Japan
Moderna Korea Limited	South Korea
Moderna Netherlands B.V.	Netherlands
Moderna Poland sp. z o.o.	Poland
Moderna Services, Inc.	Delaware
Moderna Sweden AB	Sweden
Moderna Switzerland GmbH	Switzerland
ModernaTX, Inc.	Delaware
Moderna US, Inc.	Delaware

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

- (1) Registration Statement (Form S-8 No. 333-228718) pertaining to the Moderna Therapeutics, Inc. 2016 Stock Option and Grant Plan and the Moderna, Inc. 2018 Employee Stock Purchase Plan,
- (2) Registration Statement (Form S-8 No. 333-230245) pertaining to the Moderna, Inc. 2018 Stock Option and Incentive Plan,
- (3) Registration Statement (Form S-3 No. 333-236348) of Moderna, Inc.,
- (4) Registration Statement (Form S-8 No. 333-236713) pertaining to the Moderna, Inc. 2018 Stock Option and Incentive Plan and the Moderna, Inc. 2018 Employee Stock Purchase Plan, and
- (5) Registration Statement (Form S-3 No. 333-238467) of Moderna, Inc.;

of our reports dated February 25, 2022, with respect to the consolidated financial statements of Moderna, Inc. and the effectiveness of internal control over financial reporting of Moderna, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 25, 2022

EX-31.1 Section 302 Certification of CEO

**CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

CERTIFICATIONS

I, Stéphane Bancel, certify that:

1. I have reviewed this Annual Report on Form 10-K of Moderna, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 25, 2022

By: /s/ Stéphane Bancel
Stéphane Bancel
Chief Executive Officer
(Principal Executive Officer)

EX-31.2 Section 302 Certification of CFO

**CERTIFICATION PURSUANT TO RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS ADOPTED
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

CERTIFICATIONS

I, David W. Meline, certify that:

1. I have reviewed this Annual Report on Form 10-K of Moderna, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 25, 2022

By: /s/ David W. Meline
David W. Meline
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350
AS ADOPTED PURSUANT TO SECTION 906
OF THE SARBANES-OXLEY ACT OF 2002**

I, Stéphane Bancel, Chief Executive Officer of Moderna, Inc. (Company), do hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

- the Annual Report on Form 10-K of the Company for the year ended December 31, 2021 (Annual Report) fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

- the information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 25, 2022

By: /s/ Stéphane Bancel
Stéphane Bancel
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

**CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350
AS ADOPTED PURSUANT TO SECTION 906
OF THE SARBANES-OXLEY ACT OF 2002**

I, David W. Meline, Chief Financial Officer of Moderna, Inc. (Company), do hereby certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

- the Annual Report on Form 10-K of the Company for the year ended December 31, 2021 (Annual Report) fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

- the information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 25, 2022

By: /s/ David W. Meline
David W. Meline
Chief Financial Officer
(Principal Financial Officer)

EXHIBIT 4

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Takes Key Action by Approving Second COVID-19 Vaccine

For Immediate Release:

January 31, 2022

Español (/news-events/press-announcements/actualizacion-sobre-el-coronavirus-covid-19-la-fda-toma-una-medida-clave-al-aprobar-la-segunda)

Today, the U.S. Food and Drug Administration approved a second COVID-19 vaccine. The vaccine has been known as the Moderna COVID-19 Vaccine; the approved vaccine will be marketed as Spikevax for the prevention of COVID-19 in individuals 18 years of age and older.

Key points:

- Spikevax meets the FDA's rigorous standards for safety, effectiveness and manufacturing quality required for approval.
- Moderna COVID-19 Vaccine has been available under (<https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid>) emergency use authorization (EUA) for individuals 18 years of age and older since Dec. 18, 2020.

“The FDA’s approval of Spikevax is a significant step in the fight against the COVID-19 pandemic, marking the second vaccine approved to prevent COVID-19. The public can be assured that Spikevax meets the FDA’s high standards for safety, effectiveness and manufacturing quality required of any vaccine approved for use in the United States,” said Acting FDA Commissioner Janet Woodcock, M.D. **“While hundreds of millions of doses of Moderna COVID-19 Vaccine have been administered to individuals under emergency use authorization, we understand that for some individuals, FDA approval of this vaccine may instill additional confidence in making the decision to get vaccinated.”**

Spikevax has the same formulation as the EUA Moderna COVID-19 Vaccine and is administered as a primary series of two doses, one month apart. Spikevax can be used interchangeably with the EUA Moderna COVID-19 Vaccine to provide the COVID-19 vaccination series. Moderna COVID-19 Vaccine remains available under EUA as a two-dose primary series for individuals 18 years of age and older, as a third primary series dose for individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise, and as a single booster

dose for individuals 18 years of age and older at least five months after completing a primary series of the vaccine. It is also authorized for use as a heterologous (or “mix and match”) single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine.

“The FDA’s medical and scientific experts conducted a thorough evaluation of the scientific data and information included in the application pertaining to the safety, effectiveness, and manufacturing quality of Spikevax. This includes the agency’s independent verification of analyses submitted by the company, our own analyses of the data, along with a detailed assessment of the manufacturing processes, test methods and manufacturing facilities,” said Peter Marks, M.D., Ph.D., director of the FDA’s Center for Biologics Evaluation and Research. “Safe and effective vaccines are our best defense against the COVID-19 pandemic, including currently circulating variants. The public can be assured that this vaccine was approved in keeping with the FDA’s rigorous scientific standards.”

FDA Evaluation of Effectiveness Data for Approval for Individuals 18 Years of Age and Older

The Spikevax biologics license application (BLA) builds upon the data and information that supported the EUA, such as preclinical and clinical data, as well as details of the manufacturing process and the sites where the vaccine is made. The FDA evaluates and conducts its own analyses of the data to determine whether the safety and effectiveness of the vaccine has been demonstrated and meets the standard for approval, and whether the manufacturing and facility information assure vaccine quality and consistency.

The approval of Spikevax is based on the FDA’s evaluation and analysis of follow-up safety and effectiveness data from the ongoing randomized, placebo-controlled, blinded clinical trial that supported the December 2020 EUA for the Moderna COVID-19 Vaccine and information from post EUA experience to further inform safety and effectiveness.

The updated analyses to determine effectiveness of Spikevax included 14,287 vaccine recipients and 14,164 placebo recipients 18 years of age and older who did not have evidence of SARS-CoV-2 infection prior to receiving the first dose. The data used for the analyses were accrued before the Omicron variant emerged. These data demonstrated that Spikevax was 93% effective in preventing COVID-19, with 55 cases of COVID-19 occurring in the vaccine group and 744 COVID-19 cases in the placebo group. The vaccine was also 98% effective in preventing severe disease.

FDA Evaluation of Safety Data for Approval for Individuals 18 Years of Age and Older

The FDA's safety analysis of Spikevax included approximately 15,184 vaccine recipients and 15,162 placebo recipients 18 years of age and older, more than half of these participants were followed for safety outcomes for at least four months after the second dose. Approximately 7,500 participants originally assigned to receive Spikevax in the blinded phase of the clinical trial completed safety follow-up for at least 6 months after the second dose.

The most commonly reported side effects by clinical trial participants were pain, redness and swelling at the injection site, fatigue, headache, muscle or joint pain, chills, nausea/vomiting, swollen lymph nodes under the arm and fever.

Additionally, the FDA conducted a rigorous evaluation of the post-authorization safety surveillance data pertaining to myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of tissue surrounding the heart) following vaccination with the Moderna COVID-19 Vaccine and has determined that the data demonstrate increased risks particularly within seven days following the second dose, with the observed risk highest in males 18 through 24 years of age. Available data from short-term follow-up suggest that most individuals have had resolution of symptoms. However, some individuals required intensive care support. Information is not yet available about potential long-term health outcomes. The Spikevax Prescribing Information (<https://www.fda.gov/media/155675/download>) includes a warning about these risks.

The FDA conducted its own benefit-risk assessment using modeling to predict how many symptomatic COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions and deaths from COVID-19 the vaccine in individuals 18 years of age and older would prevent versus the number of potential myocarditis/pericarditis cases, hospitalizations, ICU admissions and deaths that might be associated with the vaccine. FDA has determined that the benefits of the vaccine outweigh the risk of myocarditis and pericarditis in individuals 18 years of age and older.

The FDA is requiring the company to conduct postmarketing studies to further assess the risks of myocarditis and pericarditis following vaccination with Spikevax. These studies will include an evaluation of long-term outcomes among individuals who develop myocarditis following vaccination with Spikevax. In addition, although not FDA requirements, the company has committed to conducting additional post-marketing safety studies, including conducting a pregnancy registry study to evaluate pregnancy and infant outcomes after receipt of Spikevax during pregnancy.

The FDA granted this application Priority Review (<https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review>). The approval was granted to ModernaTX, Inc.

Related Information

- [Spikevax COVID-19 Vaccine \(https://www.fda.gov/vaccines-blood-biologics/spikevax\)](https://www.fda.gov/vaccines-blood-biologics/spikevax)
- [Moderna COVID-19 Vaccine \(https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine\)](https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine)
- [COVID-19 Vaccines \(https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines\)](https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines)

###

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Inquiries

Media:

✉ [FDA Office of Media Affairs \(mailto:fdaoma@fda.hhs.gov\)](mailto:fdaoma@fda.hhs.gov)

☎ 301-796-4540

Consumer:

☎ 888-INFO-FDA

➡ [More Press Announcements \(/news-events/newsroom/press-announcements\)](/news-events/newsroom/press-announcements)

EXHIBIT 5

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPIKEVAX safely and effectively. See full prescribing information for SPIKEVAX.

SPIKEVAX (COVID-19 Vaccine, mRNA)

Suspension for injection, for intramuscular use

Initial U.S. Approval: 2022

-----INDICATIONS AND USAGE-----

SPIKEVAX is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. (1)

-----DOSAGE AND ADMINISTRATION-----

- For intramuscular injection only.
- SPIKEVAX is administered intramuscularly as a series of two doses (0.5 mL each) one month apart. (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Suspension for injection. A single dose is 0.5 mL.

-----CONTRAINDICATIONS-----

Severe allergic reaction (e.g., anaphylaxis) to any component of SPIKEVAX. (4)

-----WARNINGS AND PRECAUTIONS-----

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. (5.2)

-----ADVERSE REACTIONS-----

- In study participants 18 through 64 years, the most commonly reported ($\geq 10\%$) adverse reactions were pain at injection site (93.3%), fatigue (71.9%), headache (68.7%), myalgia (64.8%), chills (49.7%), arthralgia (48.6%), nausea/vomiting (25.7%), axillary swelling/tenderness (22.2%), fever (17.3%), swelling at the injection site (15.4%), and erythema at the injection site (10.5%). (6.1)
- In study participants 65 years of age and older, the most commonly reported ($\geq 10\%$) adverse reactions were pain at injection site (88.3%), fatigue (64.8%), headache (53.3%), myalgia (51.8%), arthralgia (40.2%), chills (32.7%), nausea/vomiting (15.0%), swelling at the injection site (13.0%), and axillary swelling/tenderness (12.7%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ModernaTX, Inc. at 1-866-663-3762 or VAERS at 1-800-822-7967 or <http://vaers.hhs.gov>.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2022

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

2.1 Preparation for Administration

2.2 Administration

2.3 Dosing and Schedule

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

5.1 Management of Acute Allergic Reactions

5.2 Myocarditis and Pericarditis

5.3 Syncope

5.4 Altered Immunocompetence

5.5 Limitations of Vaccine Effectiveness

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Emergency Use Authorization Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIKEVAX is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Preparation for Administration

- SPIKEVAX is supplied in two presentations:
 - multiple-dose vial containing 5.5 mL
 - multiple-dose vial containing 7.5 mL
- SPIKEVAX multiple-dose vials contain a frozen suspension that does not contain a preservative and must be thawed prior to administration.
- Thaw each vial before use following the instructions below.

Multiple-Dose Vial Containing	Thaw in Refrigerator	Thaw at Room Temperature
5.5 mL	Thaw between 2°C to 8°C (36°F to 46°F) for 2 hours and 30 minutes. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw between 15°C to 25°C (59°F to 77°F) for 1 hour.
7.5 mL	Thaw between 2°C to 8°C (36°F to 46°F) for 3 hours. Let each vial stand at room temperature for 15 minutes before administering.	Alternatively, thaw between 15°C to 25°C (59°F to 77°F) for 1 hour and 30 minutes.

- After thawing, do not refreeze.
- Swirl vial gently after thawing and between each withdrawal. **Do not shake.** Do not dilute the vaccine.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- SPIKEVAX is a white to off-white suspension. It may contain white or translucent product-related particulates. Do not administer if vaccine is discolored or contains other particulate matter.
- Each dose is 0.5 mL.

- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.5 mL, discard the vial and contents. Do not pool excess vaccine from multiple vials.
- After the first dose has been withdrawn, the vial should be held between 2°C to 25°C (36°F to 77°F). Record the date and time of first use on the SPIKEVAX vial label. Discard vial after 12 hours. Do not refreeze.

2.2 Administration

Administer a single 0.5 mL dose.

2.3 Dosing and Schedule

SPIKEVAX is administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart.

There are no data available on the interchangeability of SPIKEVAX with COVID-19 vaccines from other manufacturers to complete the vaccination series. Individuals who have received one dose of SPIKEVAX should receive a second dose of SPIKEVAX to complete the vaccination series.

3 DOSAGE FORMS AND STRENGTHS

SPIKEVAX is a suspension for injection. A single dose is 0.5 mL.

4 CONTRAINDICATIONS

Do not administer SPIKEVAX to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of SPIKEVAX [*see Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of SPIKEVAX.

5.2 Myocarditis and Pericarditis

Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae. The CDC has published considerations related to myocarditis and pericarditis after vaccination,

including for vaccination of individuals with a history of myocarditis or pericarditis (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html>).

5.3 Syncope

Syncope (fainting) may occur in association with administration of injectable vaccines including SPIKEVAX. Procedures should be in place to avoid injury from fainting.

5.4 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished immune response to SPIKEVAX.

5.5 Limitations of Vaccine Effectiveness

SPIKEVAX may not protect all vaccine recipients.

6 ADVERSE REACTIONS

In study participants 18 through 64 years of age, the most commonly reported ($\geq 10\%$) adverse reactions following any dose were pain at injection site (93.3%), fatigue (71.9%), headache (68.7%), myalgia (64.8%), chills (49.7%), arthralgia (48.6%), nausea/vomiting (25.7%), axillary swelling/tenderness (22.2%), fever (17.3%), swelling at the injection site (15.4%), and erythema at the injection site (10.5%).

In study participants 65 years of age and older, the most commonly reported ($\geq 10\%$) adverse reactions following any dose were pain at injection site (88.3%), fatigue (64.8%), headache (53.3%), myalgia (51.8%), arthralgia (40.2%), chills (32.7%), nausea/vomiting (15.0%), swelling at the injection site (13.0%), and axillary swelling/tenderness (12.7%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of SPIKEVAX was evaluated in an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,346 participants 18 years of age and older who received at least one dose of SPIKEVAX (n=15,184) or placebo (n=15,162) (Study 1, NCT04470427). Upon issuance of the Emergency Use Authorization (December 18, 2020) for Moderna COVID-19 Vaccine (SPIKEVAX), participants were unblinded in a phased manner over a period of months to offer placebo participants SPIKEVAX. The median duration of follow up for safety after the second injection during the blinded phase was 4 months. The median duration of follow up for safety after the second injection including both the blinded phase and the open-label phase was 6 months.

In Study 1, the median age of the population was 52 years (range 18-95); 22,826 (75.2%) participants were 18 to 64 years of age and 7,520 (24.8%) participants were 65 years of age and older. Overall, 52.6% of the participants were male, 47.4% were female, 20.5% were Hispanic or Latino, 79.2% were White, 10.2% were African American, 4.6% were Asian, 0.8% were American Indian or Alaska Native, 0.2% were Native Hawaiian or Pacific Islander, 2.0% were other races, and 2.1% were Multiracial. Demographic characteristics were similar between participants who received SPIKEVAX and those who received placebo.

Solicited Adverse Reactions

Local and systemic adverse reactions and use of antipyretic medication were solicited in an electronic diary for 7 days following each injection (i.e., day of vaccination and the next 6 days) among participants receiving SPIKEVAX (n=15,179) and participants receiving placebo (n=15,159) with at least 1 documented dose. Events that persisted for more than 7 days were followed until resolution. Solicited adverse reactions were reported more frequently among vaccine participants than placebo participants.

The reported number and percentage of the solicited local and systemic adverse reactions by age group and dose are presented in Table 1 and Table 2, respectively.

Table 1: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 18-64 Years (Solicited Safety Set, Dose 1 and Dose 2)

	SPIKEVAX		Placebo ^a	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=11,000) n (%)	Dose 1 (N=11,402) n (%)	Dose 2 (N=10,929) n (%)
Local Adverse Reactions				
Pain	9,908 (86.9)	9,893 (89.9)	2,183 (19.1)	2,048 (18.7)
Pain, Grade 3 ^b	366 (3.2)	506 (4.6)	23 (0.2)	22 (0.2)
Axillary swelling/tenderness	1,322 (11.6)	1,777 (16.2)	567 (5.0)	474 (4.3)
Axillary swelling/tenderness, Grade 3 ^b	37 (0.3)	47 (0.4)	13 (0.1)	12 (0.1)
Swelling (hardness) ≥25 mm	766 (6.7)	1,399 (12.7)	42 (0.4)	46 (0.4)
Swelling (hardness), Grade 3 ^c	62 (0.5)	183 (1.7)	3 (<0.1)	5 (<0.1)
Erythema (redness) ≥25 mm	354 (3.1)	989 (9.0)	54 (0.5)	53 (0.5)
Erythema (redness), Grade 3 ^c	34 (0.3)	210 (1.9)	11 (<0.1)	12 (0.1)

	SPIKEVAX		Placebo ^a	
	Dose 1 (N=11,406) n (%)	Dose 2 (N=11,000) n (%)	Dose 1 (N=11,402) n (%)	Dose 2 (N=10,929) n (%)
Systemic Adverse Reactions				
Fatigue	4,385 (38.5)	7,453 (67.8)	3,281 (28.8)	2,701 (24.7)
Fatigue, Grade 3 ^d	121 (1.1)	1,178 (10.7)	83 (0.7)	88 (0.8)
Fatigue, Grade 4 ^e	1 (<0.1)	0 (0)	0 (0)	0 (0)
Headache	4,028 (35.3)	6,929 (63.0)	3,303 (29.0)	2,775 (25.4)
Headache, Grade 3 ^f	220 (1.9)	559 (5.1)	163 (1.4)	132 (1.2)
Myalgia	2,700 (23.7)	6,789 (61.7)	1,625 (14.3)	1,425 (13.0)
Myalgia, Grade 3 ^d	74 (0.6)	1,116 (10.1)	38 (0.3)	42 (0.4)
Arthralgia	1,892 (16.6)	5,010 (45.6)	1,327 (11.6)	1,180 (10.8)
Arthralgia, Grade 3 ^d	47 (0.4)	650 (5.9)	30 (0.3)	37 (0.3)
Arthralgia, Grade 4 ^e	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chills	1,050 (9.2)	5,357 (48.7)	730 (6.4)	662 (6.1)
Chills, Grade 3 ^g	17 (0.1)	164 (1.5)	8 (<0.1)	15 (0.1)
Nausea/vomiting	1,068 (9.4)	2,355 (21.4)	908 (8.0)	807 (7.4)
Nausea/vomiting, Grade 3 ^h	6 (<0.1)	11 (0.1)	8 (<0.1)	8 (<0.1)
Fever	102 (0.9)	1,909 (17.4)	37 (0.3)	38 (0.3)
Fever, Grade 3 ⁱ	10 (<0.1)	185 (1.7)	1 (<0.1)	2 (<0.1)
Fever, Grade 4 ^j	4 (<0.1)	12 (0.1)	4 (<0.1)	2 (<0.1)
Use of antipyretic or pain medication	2,656 (23.3)	6,307 (57.3)	1,523 (13.4)	1,254 (11.5)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).

^a Placebo was a saline solution.

^b Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.

^c Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.

^d Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

^e Grade 4 fatigue, arthralgia: Defined as requires emergency room visit or hospitalization.

^f Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

^g Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

^h Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

ⁱ Grade 3 fever: Defined as $\geq 39.0^{\circ} - \leq 40.0^{\circ}\text{C}$ / $\geq 102.1^{\circ} - \leq 104.0^{\circ}\text{F}$.

^j Grade 4 fever: Defined as $> 40.0^{\circ}\text{C}$ / $> 104.0^{\circ}\text{F}$.

Table 2: Number and Percentage of Participants With Solicited Local and Systemic Adverse Reactions Starting Within 7 Days* After Each Dose in Participants 65 Years and Older (Solicited Safety Set, Dose 1 and Dose 2)

	SPIKEVAX		Placebo ^a	
	Dose 1 (N=3,760) n (%)	Dose 2 (N=3,691) n (%)	Dose 1 (N=3,749) n (%)	Dose 2 (N=3,649) n (%)
Local Adverse Reactions				
Pain	2,780 (73.9)	3,071 (83.2)	482 (12.9)	438 (12.0)
Pain, Grade 3 ^b	50 (1.3)	100 (2.7)	32 (0.9)	19 (0.5)
Axillary swelling/tenderness	231 (6.1)	315 (8.5)	155 (4.1)	97 (2.7)
Axillary swelling/tenderness, Grade 3 ^b	12 (0.3)	21 (0.6)	14 (0.4)	8 (0.2)
Swelling (hardness) ≥ 25 mm	169 (4.5)	408 (11.1)	23 (0.6)	14 (0.4)
Swelling (hardness), Grade 3 ^c	20 (0.5)	72 (2.0)	3 (<0.1)	7 (0.2)
Erythema (redness) ≥ 25 mm	91 (2.4)	285 (7.7)	23 (0.6)	15 (0.4)
Erythema (redness), Grade 3 ^c	8 (0.2)	77 (2.1)	2 (<0.1)	3 (<0.1)
Systemic Adverse Reactions				
Fatigue	1,251 (33.3)	2,154 (58.4)	852 (22.7)	717 (19.6)
Fatigue, Grade 3 ^d	30 (0.8)	255 (6.9)	22 (0.6)	20 (0.5)
Headache	922 (24.5)	1,708 (46.3)	723 (19.3)	652 (17.9)
Headache, Grade 3 ^e	53 (1.4)	107 (2.9)	34 (0.9)	33 (0.9)
Myalgia	742 (19.7)	1,740 (47.2)	444 (11.9)	399 (10.9)
Myalgia, Grade 3 ^d	17 (0.5)	205 (5.6)	9 (0.2)	10 (0.3)
Arthralgia	618 (16.4)	1,293 (35.1)	457 (12.2)	399 (10.9)
Arthralgia, Grade 3 ^d	13 (0.3)	125 (3.4)	8 (0.2)	7 (0.2)
Chills	201 (5.3)	1,143 (31.0)	148 (4.0)	151 (4.1)

	SPIKEVAX		Placebo ^a	
	Dose 1 (N=3,760) n (%)	Dose 2 (N=3,691) n (%)	Dose 1 (N=3,749) n (%)	Dose 2 (N=3,649) n (%)
Chills, Grade 3 ^f	7 (0.2)	27 (0.7)	6 (0.2)	2 (<0.1)
Nausea/vomiting	194 (5.2)	439 (11.9)	167 (4.5)	134 (3.7)
Nausea/vomiting, Grade 3 ^g	4 (0.1)	10 (0.3)	5 (0.1)	3 (<0.1)
Nausea/vomiting, Grade 4 ^h	0 (0)	1 (<0.1)	0 (0)	0 (0)
Fever	10 (0.3)	367 (9.9)	7 (0.2)	5 (0.1)
Fever, Grade 3 ⁱ	1 (<0.1)	18 (0.5)	1 (<0.1)	0 (0)
Fever, Grade 4 ^j	0 (0)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Use of antipyretic or pain medication	673 (17.9)	1,548 (41.9)	477 (12.7)	331 (9.1)

* 7 days included day of vaccination and the subsequent 6 days. Events and use of antipyretic or pain medication were collected in the electronic diary (e-diary).

^a Placebo was a saline solution.

^b Grade 3 pain and axillary swelling/tenderness: Defined as any use of prescription pain reliever; prevents daily activity.

^c Grade 3 swelling and erythema: Defined as >100 mm / >10 cm.

^d Grade 3 fatigue, myalgia, arthralgia: Defined as significant; prevents daily activity.

^e Grade 3 headache: Defined as significant; any use of prescription pain reliever or prevents daily activity.

^f Grade 3 chills: Defined as prevents daily activity and requires medical intervention.

^g Grade 3 nausea/vomiting: Defined as prevents daily activity; requires outpatient intravenous hydration.

^h Grade 4 nausea/vomiting: Defined as requires emergency room visit or hospitalization for hypotensive shock.

ⁱ Grade 3 fever: Defined as $\geq 39.0^{\circ}$ – $\leq 40.0^{\circ}$ C / $\geq 102.1^{\circ}$ – $\leq 104.0^{\circ}$ F.

^j Grade 4 fever: Defined as $>40.0^{\circ}$ C / $>104.0^{\circ}$ F.

Solicited local and systemic adverse reactions reported following administration of SPIKEVAX had a median duration of 1 to 3 days.

Grade 3 solicited local adverse reactions were more frequently reported after Dose 2 than after Dose 1. Solicited systemic adverse reactions were more frequently reported by vaccine recipients after Dose 2 than after Dose 1.

In Study 1, 2.3% of participants (vaccine=347, placebo=337) had evidence of prior SARS-CoV-2 infection at baseline (immunologic or virologic evidence of prior SARS-CoV-2 infection [defined as positive RT-PCR test and/or positive Elecsys immunoassay result at Day 1]). Overall, among the 347 vaccine participants, there were no notable differences in reactogenicity compared to the 14,750 vaccine participants who had no evidence of prior SARS-CoV-2 infection at baseline (negative RT-PCR test and negative Elecsys immunoassay result at Day 1).

Unsolicited Adverse Events

Participants were monitored for unsolicited adverse events for 28 days following each dose. Serious adverse events and medically attended adverse events will be recorded for the entire study duration (2 years). Among the 30,346 participants who had received at least 1 dose of vaccine (N=15,184) or placebo (N=15,162), unsolicited adverse events that occurred within 28 days following any vaccination were reported by 31.3% of participants (n=4,752) who received SPIKEVAX and 28.6% of participants (n=4,338) who received placebo.

During the 28-day follow-up period following any dose, lymphadenopathy-related events were reported by 1.7% of vaccine recipients and 0.8% of placebo recipients. These events included lymphadenopathy, lymphadenitis, lymph node pain, vaccination-site lymphadenopathy, injection-site lymphadenopathy, and axillary mass. This imbalance is consistent with the imbalance observed for solicited axillary swelling/tenderness at the injected arm.

During the 7-day follow-up period of any vaccination, hypersensitivity events of injection site rash or injection site urticaria, likely related to vaccination, were reported by 6 participants in the SPIKEVAX group and none in the placebo group. Delayed injection site reactions that began >7 days after vaccination were reported in 1.4% of vaccine recipients and 0.7% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination.

In the blinded portion of the study, there were 8 reports of facial paralysis (including Bell's palsy) in the SPIKEVAX group, and 3 in the placebo group. In the 28-day follow-up period there were two cases of facial paralysis in the SPIKEVAX group, which occurred on 8 and 22 days, respectively, after vaccination, and one in the placebo group, which occurred 17 days after vaccination. Currently available information on facial paralysis is insufficient to determine a causal relationship with the vaccine.

In the blinded portion of the study, there were 50 reports of herpes zoster in the SPIKEVAX group, and 23 in the placebo group. In the 28-day period after any vaccination, there were 22 cases of herpes zoster in the SPIKEVAX group, and 15 in the placebo group. Currently available information on herpes zoster infection is insufficient to determine a causal relationship with the vaccine.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

Serious Adverse Events

During the blinded phase of the study, serious adverse events were reported by 1.8% (n=268) of participants who received SPIKEVAX and 1.9% (n=292) of participants who received placebo.

There were three serious adverse events of angioedema/facial swelling in the vaccine group in recipients with a history of injection of dermatological fillers. The onset of swelling was reported

1-2 days after the second dose and was likely related to vaccination.

There were no other notable patterns or imbalances between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to SPIKEVAX.

6.2 Emergency Use Authorization Experience

The following adverse reactions have been identified during emergency use authorization of SPIKEVAX (Moderna COVID-19 Vaccine). Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: myocarditis, pericarditis

Immune System Disorders: anaphylaxis

Nervous System Disorders: syncope

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SPIKEVAX during pregnancy. Women who are vaccinated with SPIKEVAX during pregnancy are encouraged to enroll in the registry by calling 1-866-MODERNA (1-866-663-3762).

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on SPIKEVAX administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study was performed in female rats administered the equivalent of a single human dose of SPIKEVAX twice prior to mating and twice during gestation. The study revealed no evidence of harm to the fetus due to the vaccine (*see Animal Data*).

Data

Animal Data

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients that are included in a 0.5 mL single human dose of SPIKEVAX was administered to female rats by the

intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. No vaccine-related fetal malformations or variations and no adverse effect on postnatal development were observed in the study.

8.2 Lactation

Risk Summary

It is not known whether SPIKEVAX is excreted in human milk. Data are not available to assess the effects of SPIKEVAX on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPIKEVAX and any potential adverse effects on the breastfed infant from SPIKEVAX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness have not been established in persons less than 18 years of age.

8.5 Geriatric Use

Clinical studies of SPIKEVAX included participants 65 years of age and older receiving vaccine or placebo, and their data contribute to the overall assessment of safety and efficacy. In a Phase 3 clinical study, 24.8% (n=7,520) of participants were 65 years of age and older and 4.6% (n=1,398) of participants were 75 years of age and older. Vaccine efficacy in participants 65 years of age and older was 91.5% (95% CI 83.2, 95.7) compared to 93.4% (95% CI 91.1, 95.1) in participants 18 to <65 years of age [*see Clinical Studies (14)*]. A lower proportion of participants 65 years of age and older reported solicited local and systemic adverse reactions compared to participants 18-64 years of age [*see Adverse Reactions (6.1)*].

11 DESCRIPTION

SPIKEVAX (COVID-19 Vaccine, mRNA) is a sterile white to off-white suspension for intramuscular injection. Each 0.5 mL dose of SPIKEVAX contains 100 mcg of nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of SARS-CoV-2 virus.

Each 0.5 mL dose of SPIKEVAX also contains the following ingredients: a total lipid content of 1.93 mg (SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.31 mg tromethamine, 1.18 mg tromethamine hydrochloride, 0.043 mg acetic acid, 0.20 mg sodium acetate trihydrate, and 43.5 mg sucrose.

SPIKEVAX does not contain a preservative.

The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The nucleoside-modified mRNA in SPIKEVAX is encapsulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SPIKEVAX has not been evaluated for carcinogenic, mutagenic potential, or impairment of male fertility in animals. A developmental toxicity study was conducted in female rats that received a vaccine formulation containing nucleoside-modified messenger ribonucleic acid (mRNA) (100 mcg) and other ingredients included in a single human dose of SPIKEVAX. No impact on female fertility was reported (*see Use in Specific Populations [8.1]*).

14 CLINICAL STUDIES

Study 1 is an ongoing Phase 3 randomized, placebo-controlled, observer-blind clinical trial to evaluate the efficacy, safety, and immunogenicity of SPIKEVAX in participants 18 years of age and older in the United States. Randomization was stratified by age and health risk: 18 to <65 years of age without comorbidities (not at risk for progression to severe COVID-19), 18 to <65 years of age with comorbidities (at risk for progression to severe COVID-19), and 65 years of age and older with or without comorbidities. Participants who were immunocompromised and those with a known history of SARS-CoV-2 infection were excluded from the study. Participants with no known history of SARS-CoV-2 infection but with positive laboratory results indicative of infection at study entry were included. The study allowed for the inclusion of participants with stable pre-existing medical conditions, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment, as well as participants with stable human immunodeficiency virus (HIV) infection. A total of 30,415 participants were randomized equally to receive 2 doses of SPIKEVAX or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 2 years after the second dose.

The primary efficacy analysis population (referred to as the Per-Protocol Set) included 28,451 participants who received two doses (at 0 and 1 month) of either SPIKEVAX (n=14,287) or placebo (n=14,164), and had a negative baseline SARS-CoV-2 status. In the Per-Protocol Set, 47.5% of participants were female, 19.7% were Hispanic or Latino; 79.7% were White, 9.7% were African American, 4.7% were Asian, and 2.0% other races. The median age of participants was 53 years (range 18-95) and 25.4% of participants were 65 years of age and older. Of the study participants in the Per-Protocol Set, 22.8% were at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease,

severe obesity, diabetes, liver disease, or HIV infection) regardless of age. There were no notable differences in demographics or pre-existing medical conditions between participants who received SPIKEVAX and those who received placebo.

The population for the vaccine efficacy analysis included participants 18 years of age and older who were enrolled from July 27, 2020, and followed for the development of COVID-19 through the data cutoff of March 26, 2021, or the Participant Decision Visit for treatment unblinding, whichever was earlier. The median length of follow-up for participants in the blinded placebo-controlled phase of the study was 4 months following Dose 2.

Efficacy Against COVID-19

COVID-19 was defined based on the following criteria: The participant must have experienced at least two of the following systemic symptoms: fever ($\geq 38^{\circ}\text{C}$ / $\geq 100.4^{\circ}\text{F}$), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. COVID-19 cases were adjudicated by a Clinical Adjudication Committee.

There were 55 COVID-19 cases in the SPIKEVAX group and 744 cases in the placebo group, with a vaccine efficacy of 93.2% (95% confidence interval of 91.0% to 94.8%) (Table 3).

SARS-CoV-2 identified in the majority of COVID-19 cases in this study were sequenced to be the B.1.2 variant. Additional SARS-CoV-2 variants identified in this study included B.1.427/B.1.429 (Epsilon), P.1 (Gamma), and P.2 (Zeta). Representation of identified variants among cases in the vaccine versus placebo recipients did not suggest decreased vaccine effectiveness against these variants.

Table 3: Vaccine Efficacy Against COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

Age Subgroup (Years)	SPIKEVAX			Placebo			% Vaccine Efficacy (95% CI) [†]
	Participant s(N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
All participants	14,287	55	9.6	14,164	744	136.6	93.2 (91.0, 94.8)
18 to <65	10,661	46	10.7	10,569	644	159.0	93.4 (91.1, 95.1)
≥65	3,626	9	6.2	3,595	100	71.7	91.5 (83.2, 95.7)

* COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms (fever [$\geq 38^{\circ}\text{C}$ / $\geq 100.4^{\circ}\text{F}$], chills, myalgia, headache, sore throat, new olfactory and taste disorder[s]) or one respiratory symptom (cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia). Cases starting 14 days after Dose 2.

[†] VE and 95% CI from the stratified Cox proportional hazard model.

Severe COVID-19 was defined based on confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, SpO₂ $\leq 93\%$ on room air at sea level or PaO₂/FIO₂ < 300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death.

Among all participants in the Per-Protocol Set analysis, which included COVID-19 cases confirmed by an adjudication committee, 2 cases of severe COVID-19 were reported in the SPIKEVAX group compared with 106 cases reported in the placebo group, with a vaccine efficacy of 98.2% (95% confidence interval of 92.8% to 99.6%) (Table 4).

Table 4: Vaccine Efficacy Against Severe COVID-19* in Participants 18 Years of Age and Older Starting 14 Days After Dose 2 per Adjudication Committee Assessments – Per-Protocol Set

SPIKEVAX			Placebo			% Vaccine Efficacy (95% CI) [†]
Participants (N)	Severe COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Participants (N)	Severe COVID-19 Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
14,287	2	0.3	14,164	106	19.1	98.2 (92.8, 99.6)

* Severe COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least two systemic symptoms or one respiratory symptom, plus any of the following: Clinical signs indicative of severe systemic illness, respiratory rate ≥ 30 per minute, heart rate ≥ 125 beats per minute, SpO₂ $\leq 93\%$ on room air at sea level or PaO₂/FIO₂ < 300 mm Hg; or respiratory failure or ARDS (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors); or significant acute renal, hepatic, or neurologic dysfunction; or admission to an intensive care unit or death. Cases starting 14 days after Dose 2.

[†] VE and 95% CI from the stratified Cox proportional hazard model.

In an exploratory analysis, occurrence of asymptomatic SARS-CoV-2 infection was assessed among participants in the Per-Protocol Set (enrolled from July 27, 2020, and followed maximally through March 26, 2021). Asymptomatic SARS-CoV-2 infection was defined as having a positive scheduled serology test based on binding antibody against SARS-CoV-2 nucleocapsid protein as measured by the Roche Elecsys immunoassay (N-serology) and/or a positive RT-PCR test for SARS-CoV-2, in the absence of any reported COVID-19 symptoms included as part of the primary efficacy endpoint case definition (described above) or symptoms included in the secondary COVID-19 endpoint case definition (fever $\geq 38^{\circ}\text{C}$ / $\geq 100.4^{\circ}\text{F}$, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, or diarrhea) at any time during the study. To assess for asymptomatic infection starting 14 days after Dose 2, all participants had scheduled blood draws for N-serology collected at the 1 month post-Dose 2 visit and the 6 months post-Dose 2 visit (if still blinded to treatment arm), and scheduled N-serology and nasopharyngeal swab for RT-PCR collection at the Participant Decision Visit for treatment unblinding.

In the Per-Protocol Set, 14,287 participants in the SPIKEVAX group and 14,164 participants in the placebo group had N-serology and/or RT-PCR results available from one or more of the pre-specified timepoints listed above. Among these participants, there were 180 cases of asymptomatic SARS-CoV-2 infection in the SPIKEVAX group compared with 399 cases in the placebo group. Limitations of this analysis include the infrequently scheduled assessments for serology and PCR testing, which may not have captured all cases of asymptomatic infections which occurred during the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIKEVAX is supplied in multiple-dose vials as follows:

NDC 80777-100-99 Carton of 10 multiple-dose vials, each vial containing 5.5 mL
NDC 80777-100-98 Carton of 10 multiple-dose vials, each vial containing 7.5 mL

During storage, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

Frozen Storage

Store frozen between -50°C to -15°C (-58°F to 5°F).

Storage after Thawing

- Storage at 2°C to 8°C (36°F to 46°F):
 - Vials may be stored refrigerated between 2°C to 8°C (36°F to 46°F) for up to 30 days prior to first use.
 - Vials should be discarded 12 hours after the first puncture.
- Storage at 8°C to 25°C (46°F to 77°F):
 - Vials may be stored between 8°C to 25°C (46°F to 77°F) for a total of 24 hours.
 - Vials should be discarded 12 hours after the first puncture.
 - Total storage at 8°C to 25°C (46°F to 77°F) must not exceed 24 hours.

Do not refreeze once thawed.

Thawed vials can be handled in room light conditions.

Transportation of Thawed Vials at 2°C to 8°C (36°F to 46°F)

If transport at -50°C to -15°C (-58°F to 5°F) is not feasible, available data support transportation of one or more thawed vials for up to 12 hours at 2°C to 8°C (36°F to 46°F) when shipped using shipping containers which have been qualified to maintain 2°C to 8°C (36°F to 46°F) and under routine road and air transport conditions with shaking and vibration minimized. Once thawed and transported at 2°C to 8°C (36°F to 46°F), vials should not be refrozen and should be stored at 2°C to 8°C (36°F to 46°F) until use.

17 PATIENT COUNSELING INFORMATION

Advise the vaccine recipient or caregiver to read the FDA-approved patient labeling.

Inform the vaccine recipient or caregiver of the potential benefits and risks of vaccination with SPIKEVAX.

Inform the vaccine recipient or caregiver of the importance of completing the two dose vaccination series.

Instruct the vaccine recipient or caregiver to report any adverse events to their healthcare

provider or to the Vaccine Adverse Event Reporting System at 1-800-822-7967 and www.vaers.hhs.gov.

There is a pregnancy exposure registry for SPIKEVAX. Encourage individuals who receive SPIKEVAX around the time of conception or while pregnant to enroll in the pregnancy exposure registry. Pregnant individuals can enroll in the pregnancy exposure registry by calling 1-866-MODERNA (1-866-663-3762).

Prior to administering the vaccine, provide the vaccine recipient the Vaccine Information Fact Sheet for Recipients and Caregivers about SPIKEVAX (COVID-19 Vaccine, mRNA) and the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) for Use in Individuals 18 Years of Age and Older. The Vaccine Information Fact Sheet for Recipients and Caregivers is available at <https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-recipients.pdf>.

This product's labeling may have been updated. For the most recent prescribing information, please visit <https://dailymed.nlm.nih.gov/dailymed/>.

Manufactured for:
Moderna US, Inc.
Cambridge, MA 02139

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SPIKEVAX is a trademark of ModernaTX, Inc.
Patent(s): www.modernatx.com/patents

US Govt. License No. 0000

Revised: 1/2022

EXHIBIT 6

MUTUAL CONFIDENTIALITY AGREEMENT

This Agreement is made as of February 7, 2014 (the "Effective Date") by and between Moderna Therapeutics Inc., a Delaware corporation, having a place of business at 200 Technology Square, Cambridge, MA 02139 ("Moderna"), and Alnylam Pharmaceuticals, Inc., a Delaware corporation, having a place of business at 300 Third Street, Cambridge, MA 02142 ("Alnylam").

1. Background. The parties intend to engage in discussions and negotiations concerning the possible establishment of a business and/or research relationship between them. In the course of such discussions and negotiations, it is anticipated that either party may disclose or deliver to the other party certain confidential or proprietary materials or information for the purpose of enabling the other party to evaluate the feasibility or desirability of such business or research relationship (the "Purpose"). The parties have entered into this Agreement in order to assure the confidentiality of such confidential or proprietary materials and information in accordance with the terms of this Agreement. As used in this Agreement, the party disclosing Confidential Information (as defined below) is referred to as the "Disclosing Party"; the party receiving such Confidential Information is referred to as the "Recipient".

2. Confidential Information. As used in this Agreement, the term "Confidential Information" shall mean all confidential or proprietary materials or information disclosed to Recipient hereunder and designated as such by the Disclosing Party or its Representatives, whether orally or in writing, prior to or at the time any such confidential or proprietary materials or information are disclosed by or on behalf of the Disclosing Party to the Recipient.

3. Disclosure and Use of Confidential Information. The Recipient shall hold in confidence, and shall not disclose to any person any of the Disclosing Party's Confidential Information except in accordance with the last sentence of this Section 3. The Recipient agrees to safeguard such Confidential Information against disclosure to others using the same degree of care as it exercises with respect to its own proprietary information and in no event less than a reasonable degree of care. The Recipient shall use such Confidential Information only for the Purpose for which it was disclosed as set forth above and shall not use or exploit such Confidential Information for its own benefit or the benefit of another without the prior written consent of the Disclosing Party. The Recipient shall disclose Confidential Information received by it under this Agreement only to those of its or its affiliates' employees, agents, legal and financial advisors, and consultants ("Representatives") who have a need to know such Confidential Information in the course of the performance of their duties with respect to the Purpose of this Agreement and who are bound by written or professional agreement to protect the confidentiality of such Confidential Information under terms at least as restrictive as the terms hereof.

4. Limitation on Obligations. The obligations of the Recipient specified in Section 3 above shall not apply, and the Recipient shall have no further obligations, with respect to any Confidential Information to the extent that such Confidential Information:

- (a) is generally known to the public at the time of disclosure or becomes generally known through no wrongful act on the part of the Recipient or its Representatives;
- (b) is in the Recipient's possession at the time of disclosure other than as a result of any prior confidential disclosure by the Disclosing Party or its affiliates or a breach of any legal obligation by Recipient or a third party;
- (c) becomes known to the Recipient through disclosure by sources other than the Disclosing Party or its affiliates having no duty of confidentiality with respect to such Confidential Information, whether to the Disclosing Party or another party, and having the legal right to disclose such Confidential Information; or
- (d) is independently developed by the Recipient without reference to or reliance upon the Confidential Information.

Notwithstanding any other provision hereof, it shall not be a violation of this Agreement for Recipient to disclose Confidential Information to the extent such disclosure is required to comply with applicable laws or governmental regulations, provided that the Recipient provides prior written notice of such disclosure to the Disclosing Party, to the extent reasonably practicable, to permit the Disclosing Party to take reasonable and lawful actions to avoid and/or minimize the extent of such disclosure.

5. Ownership of Confidential Information. The Recipient agrees that the Disclosing Party is and shall remain the exclusive owner of its Confidential Information disclosed by it hereunder and all patent, copyright, trade secret, trademark and other intellectual property rights therein. No license or conveyance of any such rights to the Recipient is granted or implied under this Agreement.

6. Return of Documents. The Recipient shall, upon the request of the Disclosing Party, return to the Disclosing Party all drawings, documents and other tangible manifestations of Confidential Information received by the Recipient pursuant to this Agreement (and all copies and reproductions thereof) except that one copy of each may be retained by the Recipient's legal department for archival purposes only and provided that neither party shall be required to destroy any computer files stored securely by such party or its affiliates that are created during automatic system back up.

7. Miscellaneous.

- (a) This Agreement constitutes the entire and exclusive agreement between the parties with respect to the subject matter hereof and supersedes all prior agreements, written or oral, between the parties relating to the subject matter of this Agreement. This Agreement may not be modified, changed or discharged, in whole or in part, except by an agreement in writing signed by the parties hereto.
- (b) This Agreement cannot be assigned except by a writing signed by both parties, provided however that either party may assign this Agreement to any of its affiliates or to a successor in connection with the merger, consolidation, sale or transfer of substantially all of its assets or business to which this Agreement relates. This Agreement will be binding upon and inure to the benefit of the parties hereto and their respective heirs, successors and permitted assigns.
- (c) The term of this Agreement during which disclosures shall be permitted shall be one year from the Effective Date (the "Term"). Each party's obligations of non-disclosure and non-use shall continue with respect to Confidential Information disclosed to it by the other party for a period of five (5) years from the expiration of the Term.
- (d) All Confidential Information is provided "AS IS" and without any warranty, express, implied or otherwise, including but not limited to any warranties regarding accuracy, completeness, performance or non-infringement of third party rights or merchantability or fitness for a particular purpose.
- (e) The provisions of this Agreement are necessary for the protection of the business and goodwill of the parties and are considered by the parties to be reasonable for such purpose. The Recipient agrees that any breach of this Agreement by Recipient may cause the Disclosing Party substantial and irreparable damages and, therefore, in the event of any such breach, in addition to other remedies which may be available, the Disclosing Party shall have the right to seek specific performance and other injunctive and equitable relief.
- (f) This Agreement shall be construed and interpreted in accordance with the laws of the Commonwealth of Massachusetts, without giving effect to the conflict of laws provisions thereof. Each party hereby submits itself for the sole purpose of this Agreement and any controversy arising hereunder to the jurisdiction of the courts located in Commonwealth of Massachusetts, and any courts of appeal therefrom, and waives any objection on the grounds of lack of jurisdiction (forum non conveniens or otherwise) to the exercise of such jurisdiction over it by any such courts.
- (g) The parties agree that they shall not disclose the terms or existence of this Agreement, any of the activities which may take place pursuant to this Agreement, the relationship formed, if any, under this Agreement or the other party's interest in the subject matter to which this Agreement relates, to anyone except its and its affiliates Representatives with a need to know. The parties agree that they will not use the name, logos, marks or trade names of the other party (or its affiliates), without limitation, in any press release or public announcement, or in the promotion of any product or service without the prior written consent of the Corporate Communications Department of such party.

- (h) This Agreement may be executed in two (2) counterparts, each of which, when fully executed, shall be deemed to be an original, and shall suffice as proof of this Agreement. Delivery of an executed counterpart or fully executed copy of this Agreement by facsimile or a .pdf data file or other scanned/electronic executed counterpart or fully executed copy by email shall be equally as effective as delivery of a manually executed counterpart or fully executed original of this Agreement. Each duplicate and counterpart shall be equally admissible in evidence, and each shall fully bind each party who has executed it. The parties to this Agreement agree that a copy of the original signature (including an electronic copy) may be used for any and all purposes for which the original signature may have been used. The parties agree they will have no rights to challenge the use or authenticity of this Agreement based solely on the absence of an original signature.
- (i) No party to this Agreement shall be obligated to enter into any further agreement with the other. In the event a business relationship relating to the Purpose goes forward, the terms and conditions of such relationship shall be set forth in a separate written agreement, mutually agreed to by the parties.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed by their duly authorized representatives.

Moderna Therapeutics, Inc.

By: 

Name: Peter Haeberli, Esq.

Title: Sr. VP IP and Legal Affairs

Alnylam Pharmaceuticals, Inc.

By: 

(Signature)

Name: Lawrence Reid, PhD
(Print or Type)

Title: Chief Business Officer

EXHIBIT 7

Moderna's Next Act Is Using mRNA vs. Flu, Zika, HIV, and Cancer

B [bloomberg.com/news/features/2021-07-14/moderna-mrna-targets-hiv-cancer-flu-zika-after-covid-vaccine](https://www.bloomberg.com/news/features/2021-07-14/moderna-mrna-targets-hiv-cancer-flu-zika-after-covid-vaccine)

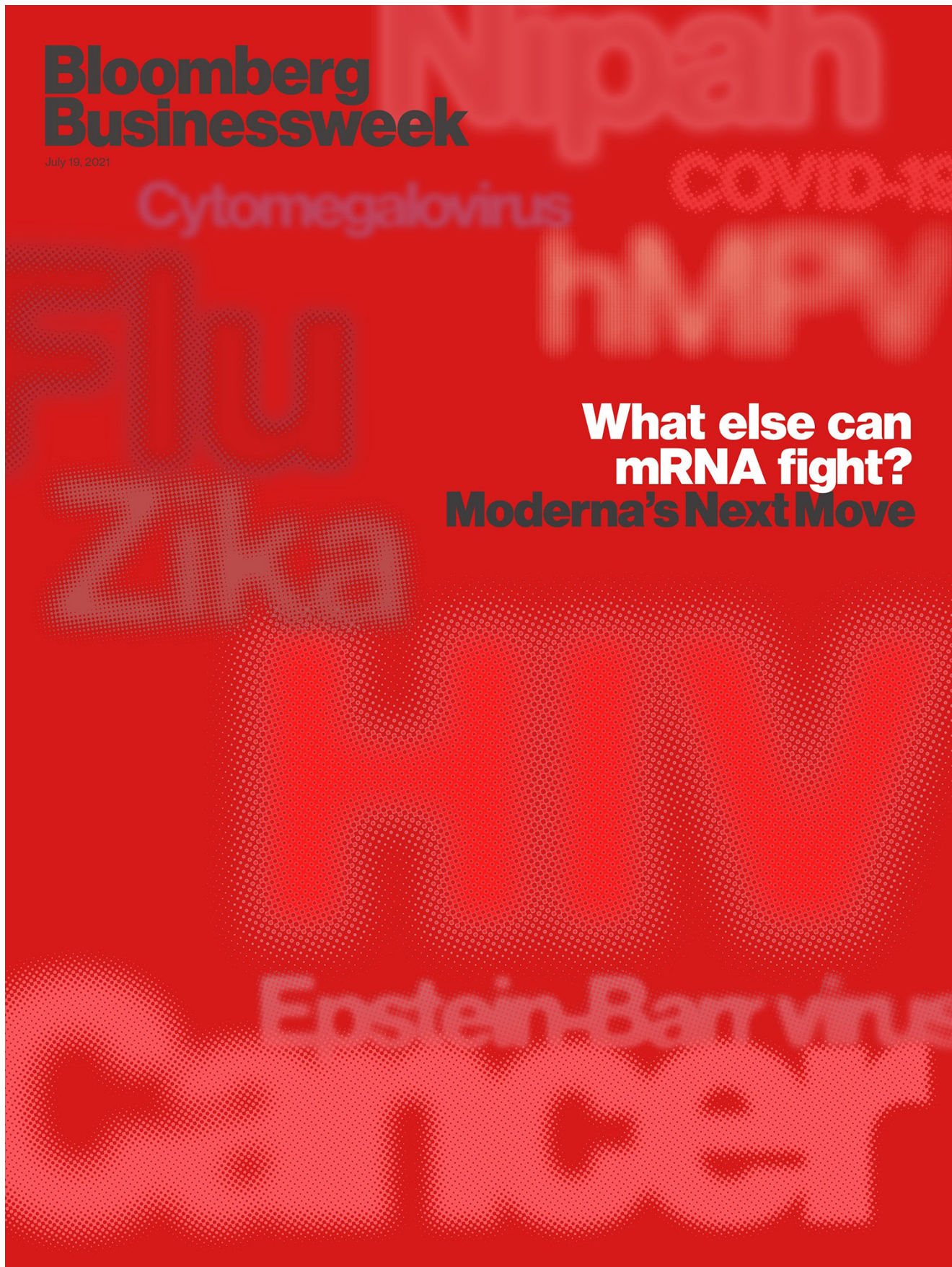
By Robert Langreth



A year ago, Moderna Inc. was an unprofitable company with no marketed products and a promising but totally unproven technology. None of its experimental drugs and vaccines had ever completed a large-scale trial. Experts were divided on how well the mRNA-based Covid-19 vaccine it was about to enter in a Phase III trial would stack up against older, more established vaccine technologies.

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This year, Moderna could deliver 1 billion doses of its Covid shot and bring in \$19 billion in revenue. It's become the rare biotech to hit the big time without being gobbled up by, or splitting profits with, a larger, more established company. Its market value—which hit \$100 billion for the first time on July 14th—exceeds that of stalwarts such as Bayer AG, the German inventor of aspirin, and biotech peers such as Biogen Inc., founded three decades prior.



Featured in *Bloomberg Businessweek*, July 19, 2021. [Subscribe now.](#)

Image: 731

The speed with which Moderna and its primary mRNA competitor, a partnership between Pfizer Inc. and BioNTech SE, devised their shots has made a major contribution to the fight to end the pandemic. With strong efficacy, steady supply, and no show-stopping safety scares (officials are carefully monitoring rare heart inflammation cases in teenagers and young adults), mRNA shots have become the vaccines of choice, at least in countries that can get them.

But for Moderna Chief Executive Officer Stéphane Bancel, the Covid vaccine is just the beginning. He's long promised that if mRNA works, it will lead to a giant new industry capable of treating most everything from heart disease to cancer to rare genetic conditions. Moderna has drugs in trials for all three of these categories, and Bancel says his company can also become a dominant vaccine maker, developing shots for emerging viruses such as Nipah and Zika, as well as better-known, hard-to-target pathogens such as HIV.

In the past 40 years, more than 50 new human viruses have been discovered. Only three have authorized vaccines. Bancel views that as an opportunity. "We are going to totally disrupt the vaccine market," he says during a late May interview at Moderna's Cambridge, Mass., headquarters, which fills a 10-story building north of the MIT campus. The Swiss drugmaker Novartis AG occupies labs in an adjacent building, and Pfizer and Merck & Co. have offices a few blocks away.





Bancel

Photographer: Adam Glanzman/Bloomberg

Bancel, who's 48, wears a pressed blue shirt, dark blue jeans, and a black Hermès belt. An avid runner, he appears even trimmer in person than on his frequent virtual conference appearances. He repeatedly jumps to his feet during the interview to graph on a whiteboard how the Covid outbreak could evolve. One chart forecasts seasonal waves, declining each passing year but still significant. Another projects the possible decay of vaccine efficacy over time, with mRNA shots like his starting in the best position but gradually declining. The take-home message coincides neatly with Moderna's business prospects: Countries may want to stockpile booster shots soon. "My mother is 72, and she has leukemia," he says. "I don't want her to go through the fall without a boost."

The company has vaccines for 10 viruses that are in, or about to be in, human trials. These include three types of Covid-19 boosters that are in midstage trials, a seasonal flu shot that began its first human study in July, and HIV shots that are slated to begin studies later this year. The furthest along besides the Covid shots combats cytomegalovirus, a ubiquitous bug that spreads through bodily fluids and is a common cause of birth defects; it's set to begin a Phase III trial this year in women of childbearing age. In the long term, Moderna is aiming to develop an annual supershot that could suppress numerous respiratory ailments, including Covid, the flu, and others. "Our goal is to give you several mRNAs in a single shot at your local CVS or GP every August or September," Bancel says.

Now comes the difficult part: delivering on that promise while keeping ahead of just about every other vaccine company in the world as they rapidly invest in mRNA. In the future, Moderna won't have the pandemic to highlight mRNA's most obvious advantages over older technologies—speed and flexibility. Future vaccines and drugs will usually have to go through the U.S. Food and Drug Administration's normal approval process, meaning longer follow-ups to gather data and 6- to 10-month review timelines. That time frame will provide space for mRNA-wielding rivals and older technologies to compete.

Pfizer, with its partner BioNTech, has become an mRNA manufacturing juggernaut and expects to produce 3 billion doses this year; it has also dominated foreign distribution of mRNA vaccines so far. Another vaccine, from CureVac NV in Germany, which took a different approach to mRNA, performed tepidly, proving only 48% effective in Phase III trial data released in June, but still another, from China's Walvax Biotechnology Co., will soon begin Phase III testing in seven countries.

More established technologies are reasserting themselves, too. On June 14, Novavax Inc. said its recombinant protein vaccine was 90% effective in a nearly 30,000-person trial in the U.S. and Mexico, with relatively few side effects—results that more or less matched those of the

best mRNA shots. Vaccine giants Sanofi and GlaxoSmithKline Plc are in Phase III trials on their own protein-based Covid vaccine, which could hit the market by yearend.

Mani Foroohar, an analyst at SVB Leerink LLC, calls Moderna's accomplishments with the Covid vaccine "truly breathtaking." But he also says it's far from certain whether such vaccines will have clear efficacy advantages with other viral diseases. And how big a role the technology could play in treating noninfectious diseases such as cancer is unknown. So though public expectations are boundless, he says, "the revenue opportunity is not."



Workers in one of Moderna's clean rooms.
Photographer: Philip Keith for Bloomberg Businessweek

The reply, for Bancel and the others pouring money into tiny RNA strands, lies in those two key advantages of speed and adaptability. At their heart, mRNA vaccines are a modular technology; they deliver the genetic code telling cells how to make the virus proteins that provoke an immune response, and the cells do the hard work from there. Now that Moderna is profitable and sitting on almost \$8 billion in cash—Bancel's own stake, including options, is worth around \$7 billion, according to the Bloomberg Billionaires Index—it can move quickly and aggressively into numerous new applications simply by changing the genetic code it puts into the mRNA. While Moderna's shot appears to be holding up well against the currently surging delta variant, for example, it's a straightforward process for the company to incorporate mutations into the vaccine if needed. "We don't have to introduce new technology or new processes," Bancel says. "It's exactly the same thing."

When Bancel left the top job at the French diagnostics company BioMérieux SA and became the second employee at Moderna—the name is a mashup of “modified” and “RNA”—a decade ago, the idea that messenger RNA could be medically useful was radical. At the time the molecule, which evolved to carry protein blueprints from DNA in the cell’s nucleus to the compartments that synthesize proteins, had a reputation among lab scientists as fragile and hard to work with. When mRNA is artificially inserted in the human body, the immune system identifies it as a threat and attacks it. And because mRNA’s function is temporary, enzymes found throughout the body can break it down. Neither are desirable outcomes for a drug or vaccine.

Starting in 2005, two researchers at the University of Pennsylvania, Katalin Karikó and Drew Weissman, managed to slightly modify mRNA so it generated less of an immune reaction in the body. The finding drew little recognition at the time, but it turned out to be a critical advance. (Katalin left Penn to join BioNTech in 2013.) In 2010 a trio of Harvard and MIT scientists funded by venture firm Flagship Pioneering picked up on the idea and founded Moderna, bringing Bancel on the next year. Moderna and BioNTech later licensed the Penn technology.

Bancel recalls telling his wife before he changed jobs that there was a 5% chance the mRNA concept would succeed, but if it did, it would be huge. When Bancel pitched Moderna’s now-president, Stephen Hoge, on the company the following year, Hoge says, his reaction was, “He’s either brilliant or crazy.” Hoge was then a McKinsey & Co. partner with a medical degree, and he was interested in doing something that would have more societal impact. He slowly came around to Bancel’s view that mRNA therapy, if it worked, “was really going to transform medicine.”

“The smart countries are saying, ‘I’d rather be two months too early than two months late’ ”

The concept behind mRNA vaccines is simple. When the shots bring those protein-making instructions to cells, they effectively turn them into microscopic vaccine factories in their own right. This allows developers to streamline what is normally a messy manufacturing process. Many flu vaccines, for example, are made inside chicken eggs, and even newer genetically engineered vaccines still require growing viral proteins inside vats of live cells. Bypassing such steps lets mRNA vaccine manufacturers shift gears fairly quickly. It also appears to be relatively easy for them to make complicated vaccines involving multiple viral proteins.

“Everything with mRNA is just simpler,” says Barney Graham, deputy director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (Niaid), whose lab has been formally collaborating with Moderna since 2017. “For me, making vaccines that are as simple as possible is the way to go.” Graham says gene-based shots such as mRNA vaccines are particularly well-suited to fighting viruses, because they seem to be adept at producing the so-called killer T-cells that destroy virus-infected cells.

Before Moderna could create an mRNA-based product, it had to crack the problem of how to protect the molecule from the body's defense systems. By modifying the RNA, the Penn researchers had figured out how to dampen the hair-trigger immune response it provoked, but their approach would be useless if it were broken down by enzymes before it could reach cells. The key to solving that problem turned out to be adding protective lipid nanoparticles to surround the mRNA molecules—essentially creating “balls of fat with little bits of RNA mixed in there,” says Kerry Benenato, a chemist who left AstraZeneca Plc to join Moderna in 2014.

When Moderna started working on this approach in 2013, it had been tried mostly on much smaller types of RNA molecules, and there were concerns about side effects. “People had decided they were toxic,” Hoge says. Nanoparticles contain synthetic fats, and in early iterations some of those fats tended to accumulate in cells, building up over time and potentially causing liver damage or other side effects.

Moderna's Revenue

Data: Compiled by Bloomberg

Benenato's assignment was to devise nanoparticles that could safely and efficiently carry the mRNA into cells, release the payload, and then quickly break down. When she started, the chemistry involved in using nanoparticles with mRNA was so unexplored that there were few published scientific papers to guide her. She and her team made one tweak after another, pinpointing changes that improved tolerability without harming their ability to deliver mRNA. By 2015, Moderna had made a breakthrough, finding a series of lipid molecules that fit the bill. “Then it was off to the races,” Benenato recalls. They patented the formulas and started deploying them in vaccines.

In its early years, Moderna had focused on therapeutics, including programs for cancer, heart disease, and other lucrative areas. The company gradually turned to vaccines as Bancel realized they would be the best way to prove mRNA technology worked. You have to inject only a couple of doses to stimulate a long-lasting immune reaction.

Working with Graham's team at NIAID, Moderna began formulating a COVID vaccine as soon as Chinese scientists released the coronavirus RNA sequence in early January 2020. Later that month, Bancel asked his manufacturing chief what it would take to make a billion vaccine doses in 2021. “He looked at me like I was insane,” Bancel recalls. The Moderna plant had never made more than 100,000 doses of anything in a year. The U.S. government agreed to pay \$955 million for the vaccine trials and initial small-scale production, but Bancel says he couldn't initially persuade any country to pay for a full scale-up. Moderna instead raised \$1.3 billion in a May 2020 stock offering for the purpose. The move allowed the company to take its leap onto the world stage—and laid the groundwork for what comes next.

Moderna produces its nanoparticles and mRNA in a former Polaroid factory in the Boston suburb of Norwood, 15 miles south of its headquarters. The plant, which opened in July 2018, has been running around the clock since November. It looks less like a factory than like a cross between a tech startup and a molecular biology lab. Dozens of operations and quality-control workers dressed in casual clothing occupy a large warren of open-layout desks in the front of the building. Covid vaccines are produced in clean rooms, some of which are visible behind glass panels in the back. There are nine of these clean rooms making the shot here, up from three in December, and six more are scheduled to be running by the end of the year. The suites, which are roughly 1,000 square feet each, were built for flexibility, with mixing reaction vessels, chromatography instruments, and other equipment on wheels so they can be easily reconfigured.



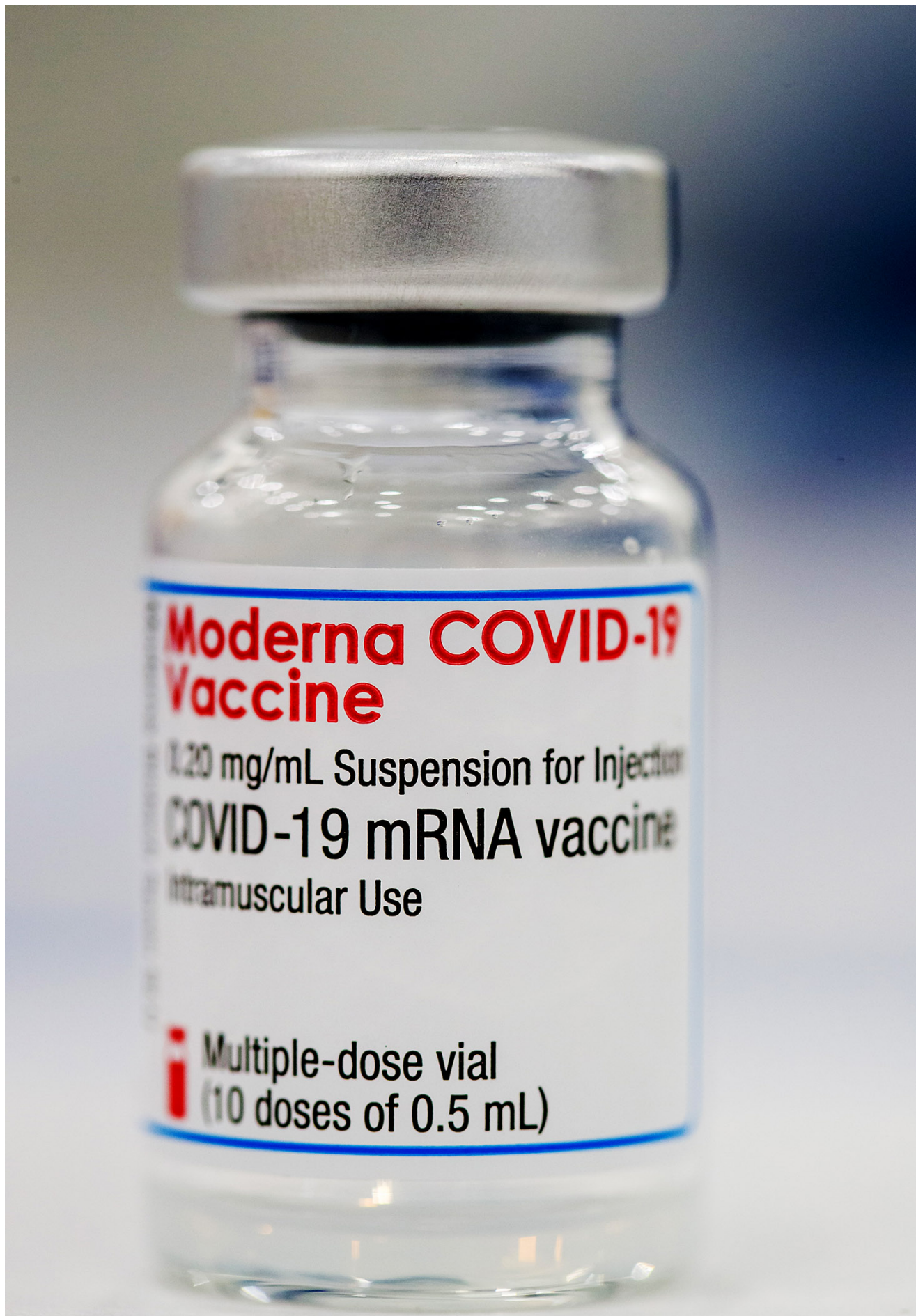
Moderna's facility in Norwood, Mass.
Photographer: Philip Keith for Bloomberg Businessweek

The process starts with pieces of DNA called plasmids that Moderna brings in from a contract manufacturer. These plasmids contain the genetic blueprint for the Covid-19 spike protein. In one set of clean rooms, the spike protein DNA is synthesized into mRNA using a technique called in vitro transcription. It's basically the laboratory version of a process that normally occurs in cell nuclei.

The mRNA solution can be made in a matter of hours, says Scott Nickerson, a senior vice president who oversees the site. It then takes several days to purify unreacted enzymes and other extraneous material. From there, the purified mRNA goes to a separate set of clean rooms, where workers spend another few days formulating it with the lipid nanoparticles. The final product is frozen in sterile bioprocessing bags, encased in a protective shell, and shipped in temperature-controlled trucks to Catalent Inc.'s plant in Bloomington, Ind. There the vaccine is diluted, put into vials, labeled, and shipped. When Moderna started making the Covid vaccine in commercial quantities last year, the process took as long as 19 days to complete. Now it takes only 10 days to prep a batch for shipping to Catalent.

Last May, Moderna signed a 10-year deal, since expanded twice, with Lonza Group AG, which is expected to produce the bulk of its European supply at factories in Switzerland and the Netherlands. Moderna also made pacts this year with Sanofi, Samsung Biologics, and Thermo Fisher Scientific to bolster the vial-filling capacity that Catalent and Laboratorios Farmacéuticos Rovi in Spain currently provide. Increasing so-called fill-finish capability will become important as a greater share of the population is vaccinated and doctors can't find enough patients to use up the larger vials now in use, which contain between 10 and 15 doses.

Moderna's production this year, 800 million to 1 billion doses, will amount to only about a third of Pfizer and BioNTech's output. Pfizer had "100 times more people" at the start of the pandemic, along with existing plants it could retool for vaccine production, Bancel says. Moderna's head count has almost doubled since last year, to 1,500. Next year, with more capacity and a significant portion of its output potentially going into booster shots and pediatric formulations that use lower doses, the company and its partners expect to produce as many as 3 billion doses, approaching Pfizer and BioNTech's projected 2022 supply of 4 billion. If Novavax meets its production goals, Sanofi's protein-based vaccine also works, and companies such as Johnson & Johnson and AstraZeneca solve their manufacturing bottlenecks, at some point next year the world could shift from being desperately short of Covid shots to swimming in them.





A used-up vial of Moderna's Covid vaccine.
Photographer: Daniel Karmann/Getty Images

As the virus settles down to a more manageable threat over the next few years, Covid vaccine sales may decline—perhaps precipitously. Morningstar Inc. analyst Karen Andersen says this market could top out at \$72 billion worldwide this year, slip to \$65 billion in 2022, and plummet to \$8 billion a year after that. The extent of the slide will depend on how many people need booster shots, how often, and whether Moderna, Pfizer, and others will be able to raise prices to compensate for a smaller market. The science on booster shots is still unsettled—it's not yet clear how often, or even whether, they'll be needed in large numbers.

Moderna has three types of boosters in Phase II trials, including a lower-dose version of its existing vaccine, one booster that's been customized against the beta variant that was first spotted in South Africa, and a third that combines both. More variants can be added if necessary. The process for the beta booster went even faster than for the original shot. Design work started on Jan. 22, with Moderna ultimately switching out some of the chemical “letters” in its original mRNA vaccine, so they correspond to the spike protein in the beta variant. Manufacturing began three days later, and the first trial dose was administered on March 10—only 47 days in all, compared with the 65 for the main vaccine.

Moderna is already cutting deals that encompass potential booster doses, including a June order from the U.S. for 200 million additional shots in late 2021 and early 2022. Despite the uncertain need for boosters, Bancel's pitch is that it's best to be prepared for an evolving virus. At an investor conference in early June, he told everyone that “the smart countries are saying, ‘I'd rather be two months too early than two months late.’”

Beyond Covid, most of Moderna's experimental vaccines remain in early stages of human trials. An exception is the shot for cytomegalovirus. No vaccine exists for this virus now, and the shot could turn into a multibillion-dollar product if it works. Moderna also plans human trials this year of a vaccine against another complicated pathogen, Epstein-Barr virus, which causes mononucleosis.

Influenza is an obvious target, and a shot for that could be combined with Covid boosters, locking them into an existing annual market. With the Pfizer-BioNTech alliance also slated to start trials on a flu shot later this year, researchers say they're hoping the mRNA vaccines can improve on existing versions, which must sometimes begin production six months in advance based on experts' assessment of which strains are likely to circulate. The shorter lead times required to make mRNA shots could, in theory, let health officials more closely match flu strains and improve upon typical 40% to 60% efficacy rates. “The mRNA vaccines have a very high likelihood of being better than the egg-based vaccines we use now,” says Andrew Pekosz, a virologist at Johns Hopkins Bloomberg School of Public Health. He adds that the shorter

lead times could “shave off months” from the process. But he notes that it’s an open question whether there would be a good economic case for mRNA-based flu vaccines if they turn out to be more expensive and only modestly better than the old ones.

Moderna is also targeting a few nasty respiratory viruses that don’t have vaccines. These include metapneumovirus, which can lead to hospitalization in infants, and respiratory syncytial virus, which causes more than 175,000 U.S. hospitalizations annually in the elderly and about 50,000 more in young children. In the latter case, Moderna’s vaccine will be competing with efforts at GlaxoSmithKline and Johnson & Johnson that draw on other technologies and are further ahead.

Hoge says Moderna could combine as many as a dozen or more viral strains in one shot. The goal is a seasonal vaccine that “eliminates the majority of the respiratory viral diseases that we all suffer from,” he says. “The only way that we’re really going to get good, broad population immunity against these respiratory viruses is if we can make it feel like your flu shot.”

The concept makes sense on paper, according to Tony Moody, a physician-researcher at the Duke Human Vaccine Institute, which is working on mRNA-based flu vaccines. Combinations are “one of the strengths of the technology,” he says. He estimates that it would cost only a few dollars more per shot to add the necessary mRNA for a given viral target. “If you could get a combo shot that gives you a degree of protection against a lot of respiratory viruses, I think there would be a market for that,” he says. It won’t be fast or easy. Researchers will first have to show that the individual vaccines work and then perform studies showing that complex combinations don’t compromise efficacy or result in troublesome side effects.

To realize its vision, Moderna will have to move quickly. Competitors are investing heavily to catch up. Sanofi said in late June it would spend €400 million (\$475 million) annually on mRNA research, focusing on stable vaccines with few side effects. With emergency authorizations unlikely in the future, considerations such as side effects and convenience will assume new prominence. Moderna is working on eliminating the complicated refrigeration requirements of its Covid shot. Future products will also have to find ways to reduce the high rates of fatigue, headache, and muscle pain produced by the shot. For the boosters, the company is testing lower doses, which may help.

How broadly mRNA can expand beyond vaccines into the far larger and more lucrative therapeutics market remains to be seen. There will be additional technical hurdles to surmount. To treat chronic diseases, for example, companies will have to prove that they can deliver the therapies to the target organs and that mRNA can be administered safely. And to develop cancer vaccines, mRNA researchers will have to solve the thorny problem of teaching the immune system to distinguish between specific tumors and healthy cells. Many previous approaches have failed.

The good news is that mRNA's adaptability also makes it easier to try out many possibilities. Within a few years, Moderna could have 60 drugs and vaccines either in human trials or nearing them, according to Bancel. If it works out the way he hopes, mRNA will make inventing vaccines and drugs a bit more like creating software. "We use the same four-letter code" for every vaccine and drug, Bancel says. "We can scale the number of products we have in development at a pace that has never been done before."

Read next: [The World's Best Hope to End the Pandemic Still Needs More Doses](#)

(Updates Moderna market value in second paragraph.)

EXHIBIT 8



Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability

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mRNA

Shelf life

Storage stability

Structure

Vaccine

ABSTRACT

A drawback of the current mRNA-lipid nanoparticle (LNP) COVID-19 vaccines is that they have to be stored at (ultra)low temperatures. Understanding the root cause of the instability of these vaccines may help to rationally improve mRNA-LNP product stability and thereby ease the temperature conditions for storage. In this review we discuss proposed structures of mRNA-LNPs, factors that impact mRNA-LNP stability and strategies to optimize mRNA-LNP product stability. Analysis of mRNA-LNP structures reveals that mRNA, the ionizable cationic lipid and water are present in the LNP core. The neutral helper lipids are mainly positioned in the outer, encapsulating, wall. mRNA hydrolysis is the determining factor for mRNA-LNP instability. It is currently unclear how water in the LNP core interacts with the mRNA and to what extent the degradation prone sites of mRNA are protected through a coat of ionizable cationic lipids. To improve the stability of mRNA-LNP vaccines, optimization of the mRNA nucleotide composition should be prioritized. Secondly, a better understanding of the milieu the mRNA is exposed to in the core of LNPs may help to rationalize adjustments to the LNP structure to preserve mRNA integrity. Moreover, drying techniques, such as lyophilization, are promising options still to be explored.

1. Introduction

Of the many COVID-19 vaccines under development, the two vaccines that have shown the most promising results in preventing COVID-19 infection represent a new class of vaccine products: they are composed of messenger ribonucleic acid (mRNA) strands encapsulated in lipid nanoparticles (LNPs). The efficacy of these mRNA vaccines developed by BioNTech/Pfizer and Moderna is about 95% (Baden et al., 2021; Polack et al., 2020) and they were the first mRNA vaccines to receive ‘emergency use authorization’ (by FDA) and ‘conditional approval’ by EMA. These mRNA COVID-19 vaccines encode the viral Spike (S) glycoprotein of SARS-CoV-2 that includes two proline substitutions (K986P and V987P mutations), in order to stabilize the prefusion conformation of the glycoprotein (Wrapp et al., 2020). Upon intramuscular (IM) administration, the LNP system enables the uptake by host cells and the delivery of mRNA inside the cytosol, where the

translation of the mRNA sequence into the S protein occurs in the ribosomes. After post-translation processing by the host cells, the S protein is presented as a membrane-bound antigen in its prefusion conformation at the cellular surface, providing the antigen target for B cells. In addition, part of the temporally produced Spike proteins enter antigen presentation pathways, providing antigen recognition by T cells via MHC presentation of T-cell epitopes (Verbeke et al., 2021). The EMA assessment report formulates the mechanism of action of mRNA vaccines at the injection site as follows: ‘Administration of LNP-formulated RNA vaccines IM results in transient local inflammation that drives recruitment of neutrophils and antigen presenting cells (APCs) to the site of delivery. Recruited APCs are capable of LNP uptake and protein expression and can subsequently migrate to the local draining lymph nodes where T cell priming occurs (EMA, 2020a).’ Because of this inherent innate immune activity, it is not necessary to formulate the mRNA vaccines with additional adjuvants. Interestingly, Pfizer/

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BioNTech and Moderna specifically use nucleoside-modified mRNA that decrease (rather than increase) the inherent mRNA immunogenicity, underlining the need to properly balance the innate immune activity of mRNA vaccines (see below). The *in vivo* antigen production post-administration that can be achieved with mRNA vaccines, together with the self-adjuvant properties of mRNA-LNP vaccines, ultimately leads to the efficient generation of neutralizing antibody responses and cellular immunity, decreasing the risk of developing COVID-19 for the vaccine recipients.

mRNA vaccines have several benefits over other types of vaccines. A general advantage of mRNA vaccines is that their development is relatively fast, as mRNA-LNPs are a true platform technology. After identification of the protective protein antigen(s) and sequencing the corresponding gene(s), the mRNA can be made within weeks (Jackson et al., 2020). As the mRNAs encoding different antigens are chemically and physically highly similar, formulation design and manufacturing processes of new mRNA vaccines follow the same steps (Petsch et al., 2012). Compared to replication deficient viral vectors, mRNA vaccines may be more efficacious for COVID-19 prevention. Unlike viral vector-based vaccines, they don't generate immunity against the carrier. In this regard mRNA vaccines are similar to deoxyribonucleic acid (DNA)-based vaccines. DNA vaccines, however, still have a minute chance of potential genome integration. Moreover, in contrast to mRNA vaccines, DNA vaccines have shown rather low immunogenicity in early clinical trials, possibly because DNA-based vaccines need to gain access to the nucleus to exert their action, complicating efficient delivery. Overall, flexible design, standardized production processes and relatively short-lived cytoplasmic presence make mRNA vaccines very powerful, especially in a pandemic situation with rapidly mutating viruses.

However, one of the greatest challenges encountered when developing mRNA vaccines is their poor stability. Currently, most mRNA vaccines are administered IM, where the mRNA that is taken up by host cells leads to antigen expression (Hassett et al., 2019). Early research on mRNA vaccines has demonstrated that naked mRNA is quickly degraded after administration (Pardi et al., 2015; Wayment-Steele et al., 2020). Consequently, over the last few years efforts were made to improve the *in vivo* stability of mRNA after administration. This led to ways to optimize the mRNA structure by slowing down its degradation (see under section 'mRNA stability'). Another successful and currently widely used approach is to encapsulate and protect the mRNA in LNPs (Pardi et al., 2015). This reduces premature mRNA degradation after administration and enhances delivery to the cytosol of antigen-presenting cells (Liang et al., 2017; Lindsay et al., 2019).

Although progress has been made to enhance the stability *in vivo* and efficacy of mRNA-LNP vaccines, much less attention has been paid to their stability during storage (Crommelin et al., 2021). In order to effectively distribute a vaccine worldwide, it should have a sufficiently long shelf life, preferably at refrigerator temperatures (2–8 °C) or above. Currently, hardly any data is available in the public domain on what happens when mRNA-LNP formulations are stored for long periods of time. Moreover, it is unclear to what extent entrapping mRNA within LNPs influences the storage stability of the mRNA vaccine. Additionally, very little is known about the structure and morphology of LNPs formulated with mRNA, the chemical stability of the LNP components and the colloidal stability of the mRNA-LNP system. What is known now is that in order to store the current mRNA COVID-19 vaccines for longer periods of time, they have to be frozen. The current mRNA COVID-19 vaccines of Moderna and BioNTech/Pfizer have to be kept between –15 and –25 °C and between –60 and –90 °C, respectively (EMA, 2020a, 2021). To date, the degradation processes and the reasons why storage temperature requirements differ, are not fully understood.

The requirement of storing the mRNA-LNPs in a frozen state hampers vaccine distribution. Especially, the very low temperature of –60 to –90 °C is a major obstacle when it comes to vaccine transport, storage and distribution among end-users worldwide. Most other vaccines can be stored at 2–8 °C. Clearly, there is a need and opportunity to find ways

of stabilizing mRNA-LNP vaccines to allow non-frozen storage. This review provides an overview of approaches to make mRNA vaccines more stable, so that they can be stored longer at less extreme temperatures. To explore the topic, the characteristics of mRNA-LNP vaccines and their influence on storage stability are discussed. This information is used to identify the reasons for mRNA vaccine instability and to explore technological options for stability improvement.

2. Overview of mRNA vaccines

The composition of mRNA-LNP vaccines is fundamental to their stability. In the development of vaccines against SARS-CoV-2, a variety of different mRNA vaccine candidates have been created. Currently, there are 10 different mRNA COVID-19 vaccines that have progressed to clinical trials (World Health Organization, 2021). The SARS-CoV-2 mRNA vaccines either use conventional mRNA or self-amplifying mRNA (SAM). There are currently three 'conventional' mRNA vaccines in use or in advanced clinical trials that encode the full S protein. These are the mRNA-1273 vaccine by Moderna, BNT162b2/Comirnaty by BioNTech/Pfizer and CVnCoV by CureVac (Table 1). A detailed comparison of these three mRNA COVID-19 vaccines including their differences and similarities in mRNA structure and LNP design has been provided in several other reviews (Kim et al., 2021; Verbeke et al., 2021). The following sections aim to give an overview of the function and characteristics of the mRNA component and the LNP delivery system in these vaccines, as they play a critical role in the stability of mRNA vaccines, both upon *in vivo* administration and during storage.

2.1. mRNA engineering for optimum *in vivo* stability and translation capacity

Because of the negative charges on its phosphate groups, mRNA is a polyanionic macromolecule in pH ranges typically used for parenterals (Lipfert et al., 2014). A first obstacle for mRNA vaccines is that naked mRNA is quickly degraded upon injection by ribonucleases (RNase), which are abundant in the extracellular environment. Second, the internalization of mRNA inside the cell is detected by intracellular RNA sensors, including endosomal Toll-like receptors (TLR) and cytoplasmic nucleic acid sensors. Binding of mRNA to these host defense receptors activates innate immune pathways, leading to the expression of hundreds of genes. One the one hand, this may provide an adjuvant effect on the vaccine potency. On the other hand, it establishes an antiviral state in cells, which strongly reduces the mRNA intracellular stability and translation (Pepini et al., 2017). Following internalization, mRNA strands need to be recruited into the ribosomes to enable the expression of the encoded protein. The protein synthesis rate and the functional half-life of mRNA can be drastically increased through mRNA engineering. The typical elements of an mRNA strand for inclusion in an mRNA vaccine are schematically presented in Fig. 1.

Many efforts have been made to increase the *in vivo* stability and translation capacity of the mRNA molecule, while avoiding unwanted innate immune activation. One prevalent idea is that this can be achieved by optimizing the regulatory regions of the mRNA: the 5' cap, poly-A tail and untranslated regions (UTRs). The UTRs are parts of the mRNA that flank the coding region of the mRNA and regulate its stability and translation. The poly-A tail also regulates stability, as its shortening and eventual removal leads to mRNA degradation. The 5' cap structure is important for protein production and the recruitment of translation initiation factors (Pardi et al., 2018). Furthermore, mRNA with maximized GC (guanine-cytosine) content in combination with codon optimization, i.e., selection of 'frequent codons' in the coding region, leads to enhanced stability and translation (Thess et al., 2015). Another critical determinant is the secondary structure of mRNA, which can be stabilized by changing the primary sequence through codon optimizations and computational tools. Building secondary structures in the mRNA –except in the 5' UTR region– by choosing 'highly structured

Table 1

Information about the three mRNA-LNP drug products that are presently used or in clinical phase III trials. For comparison reasons, drug product information for Onpattro (an siRNA-LNP drug product) has been added.

Category	siRNA	Pfizer-BioNTech mRNA vaccine	Moderna mRNA vaccine	Curevac mRNA vaccine candidate
Name product	Onpattro * patisiran	BNT162b2; Comirnaty	mRNA-1273	CVnCoV
mRNA dose; route of administration	0.3 mg/kg, intravenous	30 µg; intramuscular	100 µg; intramuscular	12 µg; intramuscular
Lipid nanoparticle components	DLin-MC3-DMA: (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) PEG2000-DMG = Alpha-(3'-{[1,2-di(myristyloxy)propanoxy]carbonylamino}propyl)-ω-methoxy, polyoxyethylene Cholesterol	0.43 mg ALC-0315 = (4-hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 0.05 mg ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 0.09 mg 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) 0.2 mg Cholesterol	SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate} PEG2000-DMG = 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine (DSPC) Cholesterol	Cationic lipid (Acuitas Therapeutics) Phospholipid Cholesterol PEG-lipid conjugate
Molar lipid ratios (%) ionizable cationic lipid : neutral lipid : cholesterol : PEG-ylated lipid	50:10:38.5:1.5	46.3:9.4:42.7:1.6	50:10:38.5:1.5	50:10:38.5:1.5
Molar N/P ratios ^a	3	6	6 ^b	6 ^b
Buffer	Potassium phosphate, monobasic, anhydrous Sodium phosphate, dibasic, heptahydrate pH ~ 7	0.01 mg Potassium dihydrogen phosphate 0.07 mg Disodium hydrogen phosphate dihydrate pH 7–8	Tris (tromethamine) pH 7–8	? pH
Other excipients	Sodium chloride Water for injection	0.01 mg Potassium chloride 0.36 mg Sodium chloride 6 mg Sucrose Water for injection	Sodium acetate Sucrose Water for injection	Saline

*NDA 210922 ONPATTRO (patisiran) Lipid Complex Injection; Addendum to Drug Product Quality Review (FDA, 2017).

^a N = ionizable cationic lipid (nitrogen), P = nucleotide (phosphate).

^b Estimate.

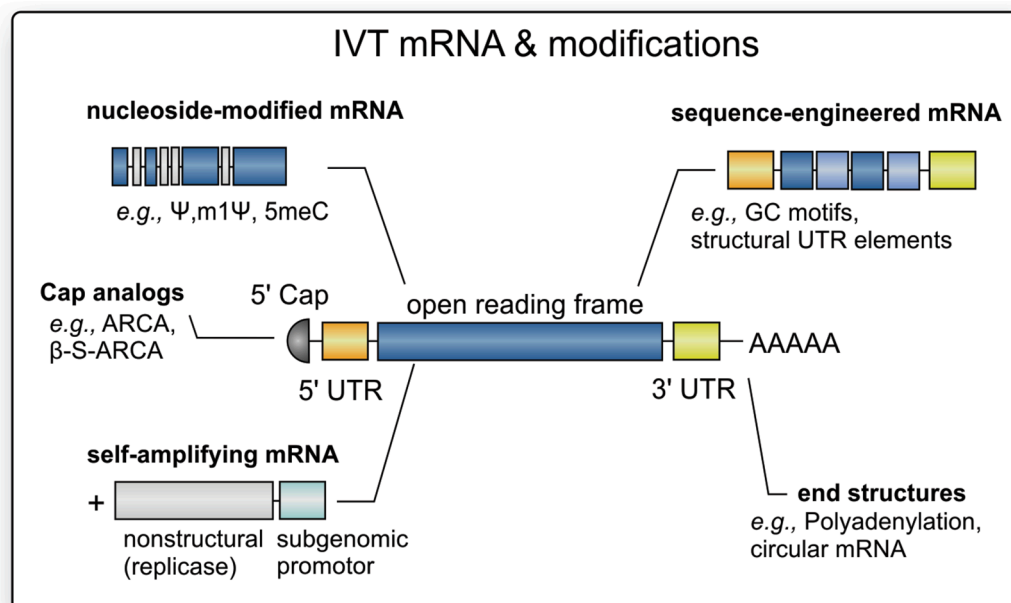


Fig. 1. Structural elements of *in vitro* transcribed (IVT) mRNA. Each of these elements can be optimized and modified in order to modulate the stability, translation capacity, and immune-stimulatory profile of mRNA. Courtesy of Verbeke et al. (2019).

coding sequences' leads to higher translation *in vivo* as well, because of a longer functional half-life (Mauger et al., 2019). Alternatively, Mauger et al. demonstrated that the incorporation of naturally occurring

modified uridines, such as the use of 1-methyl-pseudouridine (m1Ψ) instead of uridine, induces global changes in the secondary structure of mRNA which correlated with high protein expression. Importantly, the

introduction of these modified uridines inside the mRNA construct is currently the most efficient way to minimize the cellular recognition of mRNA by RNA-binding proteins that are involved in the innate immune reaction to foreign mRNA. This, in turn, enhances biological stability and translational capacity, while reducing the reactogenicity of mRNA vaccines. Moreover, there are also indications that m¹Ψ increases base stacking and the melting point of mRNA, thereby making mRNA more stable (Mauger et al., 2019; Zhao and He, 2015). This could mean that the incorporation of 1mΨ, as is done for the COVID-19 vaccines from Moderna and BioNTech/Pfizer, also affects the stability of mRNA before administration. CureVac followed a different path, as outlined by Thess et al. (Thess et al., 2015). An interesting analysis of the choices CureVac made in engineering the CVnCoV mRNA was recently published (Hubert, 2021). However, even when these structural elements are optimized, IM injection of naked mRNA through a syringe does not lead to a robust immune response, probably because of the poor cell transfection capacity of naked mRNA and the susceptibility to RNase (Pardi et al., 2015). Importantly, this illustrates that optimization of only the mRNA structure is not sufficient for creating effective mRNA vaccines: additional protection and delivery systems are needed (Kauffman et al., 2016; Sahin et al., 2014).

The other type of mRNA vaccines, SAMs, do not only encode the target antigen but also RNA polymerase encoding 'self-amplifying' factors derived from Alphavirus. Typically, they consist of 9 kb mRNA nucleotides compared to 2–4 kb for non-replicating mRNA vaccines. The SAM vaccine candidates were developed with the intent of forgoing the typical 'prime-boost' regimen of a two-dose strategy and instead focusing on a single injection per recipient. Because of their replication competence, the injected dose for SAM vaccines is lower than for conventional mRNA vaccines and one dose might be sufficient for protection (Erasmus et al., 2020; Vogel et al., 2018). When SAMs are translated in the host cell, an RNA replicase synthesizes negative-sense RNA intermediates complementary to the coding mRNA template (Fig. 1). These are in turn transcribed to many coding mRNA molecules, leading to prolonged and enhanced antigen expression (Bloom et al., 2020). Both SAM vaccines encode the full S protein and the highest dose for these vaccines in clinical trials was more than tenfold lower than the typical doses used for the conventional mRNA vaccines (Ward and McCormack, 2021). The two SAM vaccines in clinical development are nCoVsaRNA by the Imperial College London and ARCT-021 by Arcturus/Duke-NUS (both as mRNA-LNP).

2.2. LNPs as delivery system

To overcome these transfection problems with naked mRNA, protecting delivery systems have been developed. Currently, the leading mRNA COVID-19 vaccines (Table 1) are all utilizing LNP technology. This illustrates the successes achieved with this type of nanoparticle to stabilize mRNA and successfully deliver it into cells (Pardi et al., 2015). The LNPs in mRNA COVID-19 vaccines consist of four main components (cf. Table 1): a neutral phospholipid, cholesterol, a polyethylene-glycol (PEG)-lipid, and an ionizable cationic lipid. The latter contains positively charged ionizable amine groups (at low pH) to interact with the anionic mRNA during particle formation and also facilitate membrane fusion during internalization (Evers et al., 2018; Reichmuth et al., 2016). In addition, PEG-lipid is used to control the particle size and act as a steric barrier to prevent aggregation during storage. Together with the mRNA, these components form particles of about 60–100 nm in size by using a rapid mixing production technique (Evers et al., 2018). The SARS-CoV-2 vaccine candidates nCoVsaRNA and ARCoV, for example, have average particle sizes of 75 nm and 89 nm, respectively (McKay et al., 2020; N.-N. Zhang et al., 2020).

A key aspect of LNPs and the characteristic that makes them different from liposomes (spherical vesicles with at least one lipid bilayer and an aqueous core) is the presence of lipids in the core, although data from several studies indicate that water is also present to some extent (Arteta

et al., 2018; Kulkarni et al., 2018; Brader et al., 2021). This would mean that the mRNA could be exposed to an aqueous environment, even when it is encapsulated. This type of core structure has been previously found in both unloaded and siRNA (small interfering RNA) containing LNPs, as demonstrated by cryogenic transmission electron microscopy (cryo-TEM) (Kulkarni et al., 2019, 2018). Similarly, studies of mRNA-LNPs have shown electron dense cores (Fig. 2) (Arteta et al., 2018; Eygeris et al., 2020; Leung et al., 2015; Patel et al., 2020; Tanaka et al., 2020). Thionine was used for cryo-TEM contrast enhancement (Brader et al., 2021).

Although their lipid core is a common feature of mRNA-LNPs, characteristics of the exact structure of this core and its dependence on lipid ingredients (molar ratios) and the localization of the mRNA are still under debate (see Fig. 3). mRNA is certainly located inside the LNPs, as determined by the RiboGreen assay. RiboGreen is a dye that exhibits fluorescence when bound to single stranded mRNA, but cannot enter the LNPs. In mRNA-LNP formulations, such as those used in mRNA vaccines, the fraction of accessible mRNA is very low (Arteta et al., 2018; Patel et al., 2020) and thus, encapsulation efficiencies, derived from RiboGreen assays, are typically > 90%. Taken together, the cryo-TEM (Fig. 2) and encapsulation evidence shows that the mRNA-LNPs form nanoparticles with encapsulated mRNA that is protected from the external medium. There are 3 models proposed for the structure of mRNA encapsulated by LNPs; these mainly originate from siRNA-LNPs analysis (Fig. 3).

The dawn of mRNA vacca limitation of this is that the encapsulated cargo affects the structure of LNPs: siRNA is very different from mRNA in structure and size (Table 2) and the molar N/P (ionizable cationic lipid over phosphate) molar ratios differ, 3 versus 6, respectively (Table 1). mRNA is at least 100-fold larger than siRNA and this affects the structure of the LNPs. Besides, there are indications that mRNA is located in the core of the LNPs and siRNA more towards the surface and mRNA can form 'blebs' (Fig. 2) (Viger-Gravel et al., 2018). The composition of the bleb part of the LNP is a matter of debate (Leung et al., 2015; Brader et al., 2021). The latter state: "mRNA can dissociate from the charged lipid to reside within a solvent-filled bleb compartment."

The multilamellar vesicle model for mRNA-LNPs (Fig. 3A) is unlikely to be correct. It does not correspond to the electron dense cores found by TEM of the mRNA-LNPs. Currently, most researchers hold the view that

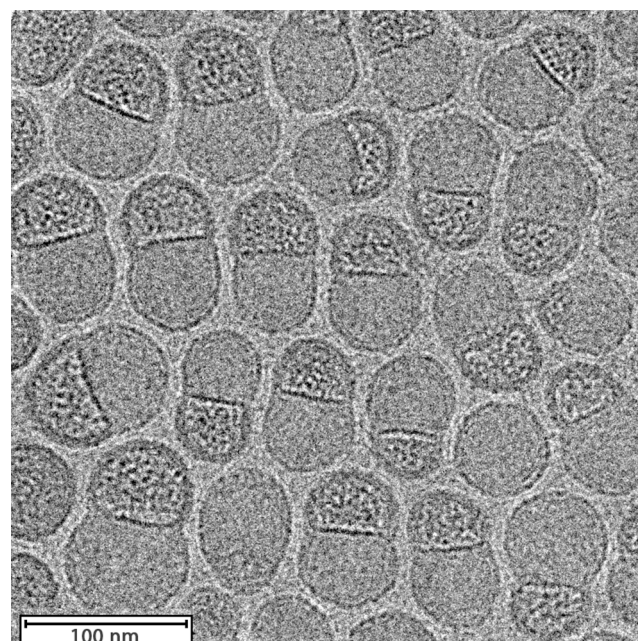


Fig. 2. Cryo-TEM image of mRNA-LNP showing 'bleb' structures with distinctly different electron density. Adapted from Brader et al. (2021) with permission.

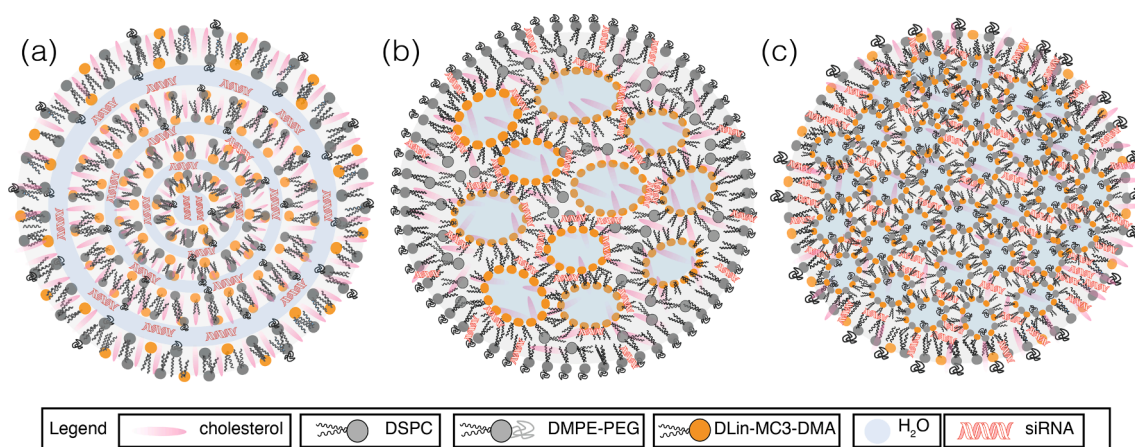


Fig. 3. Schematic representation of the proposed models for siRNA-LNP and mRNA-LNP structure. A: multilamellar vesicles; B: nanostructure core; C: homogeneous core shell as discussed by Viger-Gravel et al. (2018). Courtesy of the authors.

Table 2

Differences between mRNA and siRNA molecules.

	mRNA	siRNA
Molecular weight (g/mol)	$\geq 10^6$	10^4
Molecular conformation	Single stranded	Double stranded
5' end	5' cap	Phosphorylated 5' end
3' end	Poly-A tail	Hydroxylated 3' end

mRNA-LNPs are best described by the core-shell model (Fig. 3B & C). This means that the nanoparticles have a surface layer and an amorphous, isotropic core. Viger-Gravel et al. used NMR spectroscopy to elucidate an LNP structure and they make the case that two types of core are possible (Viger-Gravel et al., 2018). They describe the model of an amorphous core containing water pores surrounded by inverted cationic lipids (Fig. 3B). They also postulate that the lipids in the core could be homogeneously dispersed with small water pockets in between (Fig. 3C). The latter corresponds more to the experimental results for their siRNA-LNPs and mRNA-LNPs.

Arteta et al. based their mRNA-LNP structure-model on cryo-TEM, small-angle X-ray scattering (SAXS) and small-angle neutron scattering (SANS) measurements. They found that 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and PEG-lipid as well as part of the ionizable cationic lipid and cholesterol are located on the surface of the LNPs. Inside the core, the main part of the ionizable cationic lipid, cholesterol (dependent on its concentration), water and mRNA are present. Interestingly, their research indicates that the isotropic LNP core consists for 24% (volume fraction) of water. They propose that mRNA is located inside water cylinders, which are surrounded by cationic lipids (Fig. 4). This would mean that the mRNA is—at least partly—exposed to water inside the LNPs, which likely contributes to its instability upon storage under non-frozen conditions (Arteta et al., 2018). Comparable results were reported by Sebastiani et al. (2021).

It would, therefore, be interesting to study how mRNA interacts with water and ionizable cationic lipids in the LNP. mRNA is hydrophilic; it can interact electrostatically and through hydrogen bonds with ionizable cationic lipids (apparent $pK_a < 6.5$) (Buschmann et al., 2021). This depends on the pH inside the LNP. If the LNP shells are permeable to protons—which is likely, as ionized dyes such as 2-(p-toluidino)-6-naphthalene sulfonic acid (TNS) and thionine can enter the LNP core (Jayaraman et al., 2012; Brader et al., 2021)—the pH would be similar to the rest of the formulation, around 7 to 8, meaning that most of the ionizable cationic lipids would be uncharged. However, as the ionizable cationic lipids are stacked in the core, they may show polyelectrolyte behavior, leading to deviations of the Henderson-Hasselbalch equation, i.e., ‘smearing out’ of the titration curve (Pierrat and Lebeau, 2015).

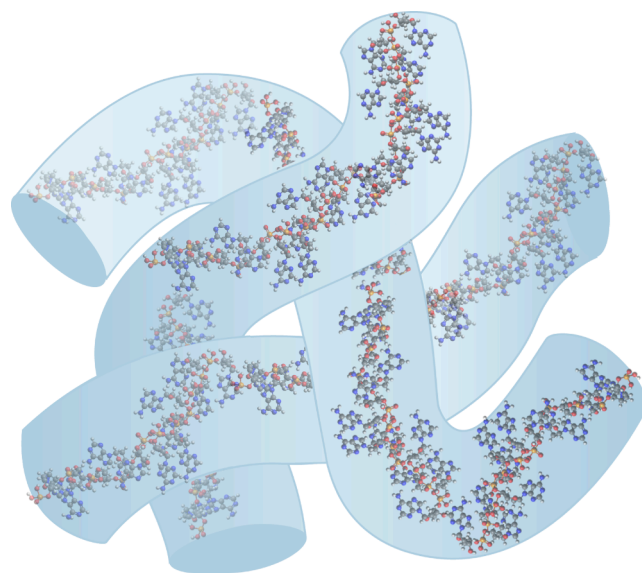


Fig. 4. Schematic representation of the mRNA-water cylinders in the core of mRNA-LNPs (Arteta et al., 2018). Courtesy of the authors.

Moreover, interaction between the mRNA and the ionizable cationic lipids might affect the ionization behavior. For siRNA only weak electrostatic interactions were found with the ionizable cationic lipid, indicating that at least for siRNA-LNP formulations the pH inside approaches or equals the pH outside (Viger-Gravel et al., 2018). For mRNA-LNPs, no such experimental studies have been performed yet. A molecular dynamics simulation study of the complexation of mRNA and a cationic lipid demonstrated lipid-lipid cluster formation and lipid-mRNA cluster formation. Both electrostatic and hydrogen bonds were driving the cationic lipid and mRNA interactions (Rissanou et al., 2020).

Another interesting finding by Arteta et al. is that the shell of their mRNA-LNPs is a monolayer (Arteta et al., 2018; Verbeke et al., 2019). Other researchers propose that the outer shell of mRNA-LNPs consists of one or multiple bilayers, based on cryo-TEM analysis (Fig. 2) (Patel et al., 2020; Tanaka et al., 2020) or SANS (Sebastiani et al., 2021). These findings indicate that assessment of the nature of the mRNA-LNP shell with these techniques is difficult and/or that multiple types of mRNA-LNP structures may exist, dependent on, e.g., the nature of the lipids and the preparation protocol for the mRNA-LNPs. This, in turn, could have implications for the stability of different formulations. In conclusion, questions remain around the structure of mRNA-LNPs and the

interactions between the encapsulated mRNA and the various lipid components.

Analysis of the components of the various mRNA-COVID-19 vaccines has shown that there are common features, but also significant differences (Table 1). The LNP formulation, the use of modified-nucleosides, the GC content and the differences in length between the conventional mRNA and SAM vaccines might influence the physical and chemical stability of these mRNA-COVID-19 vaccines during storage.

3. In vitro stability of mRNA vaccines

As mentioned in the introduction, one of the main obstacles for the distribution of the currently approved mRNA-COVID-19 vaccines is that they have to be stored in frozen form (cf. Crommelin et al., 2021). At refrigerator temperatures, 2–8 °C, the Pfizer/BioNTech and Moderna vaccines are stable for 5 and 30 days, respectively. Both companies provide detailed handling instructions for the end-user (EMA, 2020b, 2021). Interestingly, the vaccine candidate by CureVac is reported to be stable for 3 months at refrigerator temperatures and at –60 °C (CureVac, 2020). These are the only manufacturers who have released their long-term storage conditions at present. Such temperature requirements severely impact the logistics of the storage, transport, and distribution of these vaccines. However, to date little information on optimization of the stability of mRNA vaccines can be found in the public domain. This section aims to give an overview of the factors that influence the stability of the components of mRNA-LNP vaccines and discuss the methods to analyze this stability.

3.1. mRNA stability

One factor that strongly influences the required storage conditions is the stability of the mRNA. As discussed above under Section 2.1, the structure of the mRNA molecule is specifically designed to increase the translation of the target antigen *in vivo*. A special feature of mRNA is that even one change (strand break, or oxidation of the bases) in the long mRNA strand (typically between 1000 and 5000 nucleotides long) can stop translation (Klauer and van Hoof, 2012). This makes mRNA vaccines quite different from other vaccines in which small changes of the antigens do not necessarily have a measurable effect on their efficacy. Consequently, for mRNA vaccines, it is critical to monitor the integrity of the full molecule.

There are several ways in which mRNA degradation can occur; one can discern chemical and physical degradation. Chemical degradation encompasses the modifications of bonds in the mRNA molecule. Physical instability includes denaturation (loss of secondary and tertiary structure), which has different –likely less significant– consequences for the activity of mRNA than denaturation has for the activity of protein biologics. However, denaturation also comprises processes such as aggregation and precipitation, which negatively affect mRNA translation. In a review on the stability of nucleic acids Pogocki and Schöneich state

that chemical degradation plays a larger role in the degradation of small nucleic acids than physical instability and that is probably even more true for large structures such as mRNA (Pogocki and Schöneich, 2000).

Chemical degradation of mRNA *in vitro* mainly occurs through hydrolysis and oxidation. Hydrolysis predominantly occurs via the phosphodiester bonds that form the backbone of the mRNA molecule (Fig. 5). The 2' OH group on the ribose plays a crucial role as the transesterification reaction leading to a mRNA strand break starts by a nucleophilic attack by the 2'OH group on the phosphate ester bond leading to a break at the P-O5' ester bond (Fig. 5). This process requires water and can be catalyzed by nucleases, but also by the mRNA molecule itself and other exogenous factors like Brønsted acids and bases (Houseley and Tollervey, 2009; Pogocki and Schöneich, 2000). In two publications on mRNA hydrolysis the authors state that the base sequence and secondary structure of mRNA influence the rate of hydrolysis (Kaukinen et al., 2002; Mikkola et al., 2001). Specifically, base-stacking may decrease the cleavage rate of phosphodiester bonds. The 'average unpaired probability' of an mRNA molecule can be minimized. Specially designed algorithms that select nucleotide sequences for single stranded mRNA with maximum double stranded regions are available. *In vitro* stability is claimed to be significantly improved following this approach (Wayment-Steele et al., 2020). A difference between the CureVac, Pfizer/BioNTech and Moderna vaccines is that the latter two have single nucleoside incorporations of 1-methyl-pseudouridine. A previous study has shown that this modification improves RNA secondary structure stability (Mauger et al., 2019). CureVac uses GC-enrichment, which should have a similar effect (Hubert, 2021; Zhang et al., 2011).

Oxidation, in contrast, affects the nucleobases and to a lesser extent the sugar groups of the mRNA's ribose units. Oxidation can lead to the cleavage of bases, strand break and the alteration of the secondary structure of the mRNA (Pogocki and Schöneich, 2000). However, as stated before, hydrolysis appears to be accepted as the main factor driving mRNA degradation (Fabre et al., 2014).

3.2. Analyzing mRNA stability

As the integrity and purity of the mRNA are essential to safeguard efficacy and safety of mRNA vaccines, it is important to have tools to monitor these aspects. There are various attributes of the mRNA molecules that collectively determine whether the product can be used. The review by Poveda *et al.* highlights these attributes and briefly touches upon approaches that are used in general to measure and monitor them (Poveda et al., 2019).

Table 3 provides a comprehensive list of analytical methods to determine and monitor quality attributes and stability of mRNA vaccine bulk drug substance and final drug product. Quality specifications for the presently accepted mRNA-LNP COVID-19 products are still not available in the public domain. Leaked documents (through a cyber-attack of the EMA, just before the approval date in the UK and the

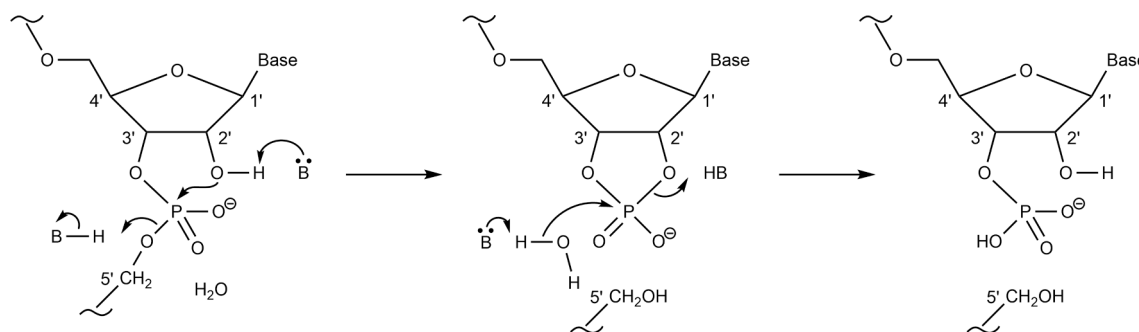


Fig. 5. Base-catalyzed intramolecular hydrolysis of the phosphodiester bond in RNA by way of a 2',3'-cyclic phosphite. B denotes a Brønsted base. Redrawn from Pogocki and Schöneich (2000).

Table 3

Assays to determine and monitor mRNA drug substance and mRNA-LNP drug product quality attributes and stability.¹⁾

Assay ²⁾	Attribute
Characterizing DNA templates and RNA transcripts	
DNA template sequencing/mRNA sequencing	Identification of mRNA
UV spectroscopy (A260 nm, A260/A280, A260/A230)	Quantification - purity dependent
Fluorescence-based assays (e.g., residual DNA)	Quantification - purity dependent
Agarose/acrylamide electrophoresis	Molecular mass, RNA integrity and quantification
Reverse transcriptase qPCR	Identification and quantification of mRNA
Western blot for dsRNA	Quality assessment
mRNA capping analysis	Quality assessment
mRNA polyadenylated tail analysis	Quality assessment
Chromatographic assays: RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC	Quantity and quality assessment
Characterizing mRNA-encoded translation products	
In vitro translation - cell free medium	Translation into target protein
Messenger RNA evaluation using various cell-based systems	Translation product analysis and potential toxicity assay
Characterizing mRNA-lipid complexes	
DLS	Particle size (distribution)
Laser Doppler electrophoresis	Zeta potential
NTA/TRPS	Particle size (distribution)
SE-HPLC(MALS)	Particle size distribution; assessing bound/unbound mRNA
Microscopy (cryo TEM, ESEM, AFM)	Nanoparticle morphology, particle size (distribution)
Gel or capillary electrophoresis	Assessing bound/unbound mRNA and surface charge
Chromatographic assays: RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC / mass spectrometry	Quantification and integrity of lipids and/or mRNA; for some: assessing bound/unbound mRNA and molar mass
Fluorescent dyes	Encapsulation efficiency
General pharmaceutical tests	
	Appearance, pH, osmolality, endotoxin concentration, sterility

¹⁾ Adapted from [Poveda et al., 2019](#); [Muralidhara et al., 2016](#); [Fan et al., 2021](#); [Crommelin et al., 2021](#).

²⁾ Abbreviations: AF4, asymmetrical flow field-flow fractionation; AFM, atomic force microscopy; dsDNA, double stranded DNA; DLS, dynamic light scattering; ESEM, environmental scanning electron microscopy; IEX-HPLC, ion-exchange high performance liquid chromatography; IP-HPLC, ion-pair high performance liquid chromatography; MALS, multi-angle light scattering; NTA, nanoparticle tracking analysis; qPCR, quantitative polymerase chain reaction; RP-HPLC, reversed-phase high performance liquid chromatography; SE-HPLC, size-exclusion high performance liquid chromatography; TEM, transmission electron microscopy; TRPS, tunable resistive pulse sensing.

USA), which contain classified information on the quality of Comirnaty, mention percentages of mRNA integrity between 70 and 75% ([Tinari, 2021](#)) and the assessment report from the EMA reads: 'the quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable.'

Here we elaborate on the techniques that are applicable for studying the integrity of mRNA and used for quality control (QC). An overview of quality documentation required by EU authorities for an Investigational Medicinal Products Dossier (IMPd) with a focus on mRNA vaccines is given by Schmidt and the interested reader is referred to that informative document for details ([Schmid, 2017](#)). Because many of the described methods are intended for assaying naked mRNA, whereas mRNA vaccines for COVID-19 are encapsulated in LNPs, for some assays the mRNA first needs to be released and isolated from the LNP. Potential effects of this isolation process can be taken into account by including proper controls.

Gel electrophoresis is a frequently used technique that can give information on the size and the integrity of the mRNA. When mRNA degrades and strand breaks occur, the mRNA strand becomes shorter. As a result, the intensity of the band at the expected mRNA length will decrease or the band will broaden, while new bands may appear. Using this approach [Démoulin et al.](#) analyzed the quality of SAM under RNase free conditions ([Démoulin et al., 2017](#)). Based on the gel electrophoresis data, they were able to determine whether the mRNA is of acceptable quality and stable. Commercial electrophoresis equipment is now available for high-throughput analysis of mRNA ([Pocernich et al., 2019](#)).

Recently, [Zhang et al.](#) showed that fluorescence correlation spectroscopy (FCS) can be used to monitor changes in mRNA size ([H. Zhang et al., 2020](#)). The Brownian motion of fluorescent mRNA gives an indication of its molecular weight. This technique, however, needs a fluorescent label, is not more accurate than gel electrophoresis and only detects mRNA degradation involving substantial changes in molecular weight, e.g., strand breaks.

Throughout the (bio)pharmaceutical industry chromatographic techniques form a powerful platform to monitor purity and stability of active pharmaceutical ingredients and drug products. However, the development of HPLC techniques for establishing purity and stability of mRNA molecules has been slow so far. Successful protocols for analyzing large mRNA molecules can be found in the patent literature as well as in publications where RP-HPLC, SE-HPLC, IP-HPLC and IEX-HPLC methods are described ([Issa and Packer, 2019](#); [Kanavarioti, 2019](#); [Spivak et al., 2014](#)). Some of these techniques can also be used for mRNA purification purposes ([Kim et al., 2007](#); [Levine et al., 2019](#)). IEX-HPLC can be used for measuring free and LNP encapsulated mRNA. An orthogonal technique to establish the same parameter is the earlier mentioned RiboGreen technique. Different outcomes, however, were found for the same mRNA-LNP product; the IEX-HPLC outcome correlated better with the *in vivo* readout than the RiboGreen data. This illustrates that even established techniques like the RiboGreen assay should be carefully validated on a case-by-case basis ([Schariter et al., 2019](#)).

mRNA degradation can also be analyzed by using the reverse transcription quantitative polymerase chain reaction (RT-qPCR). This approach quantifies the total amount of mRNA that can be transcribed into intact cDNA targets for PCR. This means that all degradation that prevents this can be quantified indirectly. In their evaluation of this technique, [Brisco and Morley](#) argue that it gives reliable quantitative results ([Brisco and Morley, 2012](#)). Another advantage of this method is that all types of degradation that affect transcription are taken into account, whereas the previously discussed techniques only look at mRNA size. However, RT-qPCR sometimes is less reliable due to the error rate of the enzymes that are used ([Schmid, 2017](#)). Other disadvantages of this approach are that it is not widely used and the different types of degradation cannot be distinguished from each other.

mRNA expression *in vitro* (in cells) is also used to analyze the integrity of mRNA ([Zhang et al., 2020b](#); [Zhao et al., 2020](#)). By using mRNA that encodes a fluorescent protein, the mRNA integrity can indirectly be determined by measuring the fluorescence signal. This approach can assist in providing guiding principles for bioactive mRNA-LNP design and formulation development studies. Alternatively, the translation efficacy of mRNA encoding non-fluorescent antigens can be determined using an enzyme-linked immunosorbent assay (ELISA), or western blotting techniques as has been used previously to analyze the stability of mRNA encoding the receptor-binding domain (RBD) of SARS-CoV-2 ([Zhang et al., 2020b](#)). Advantages of this approach are that it gives the sum of the overall integrity of the formulation and everything that can influence the transcription of the mRNA. Disadvantages of this method are that it is not very precise, unable to show the type of mRNA damage, and time-consuming.

3.3. LNP stability

Besides mRNA integrity, stability of LNPs is critical for the quality of mRNA-LNP vaccines. No information on LNP stability tests could be found for the present mRNA COVID-19 vaccines, but the siRNA-LNP formulation of Onpattro (patisiran) has a three-year shelf life when kept between 2° and 8 °C (EMA, 2018). There is a warning in this SMPC text that the dispersion should not be frozen. The composition of the Onpattro LNP system is: DLin-MC3-DMA, as ionizable cationic lipid: DSPC: cholesterol: PEG2000-C-DMG (see table 1) (mol-ratio 50:10:38.5:1.5 mol%); they are composition-wise similar to the LNPs in Comirnaty and mRNA-1273. A study on siRNA-LNPs composed of the lipidoid 306O₁₃ instead of DLin-MC3-DMA, showed that in aqueous conditions the formulation remained stable at 2 °C for 156 days at pH 7 (Ball et al., 2016). Particle size and siRNA encapsulation for this formulation did not significantly change. Complementary research by Suzuki et al. showed that siRNA-LNPs are stable over the experimental period, i.e. 1.5 years, at 4 °C (Suzuki et al., 2015). Altogether, these data strongly indicate that instability of the mRNA, rather than LNP instability, determines the storage conditions and shelf life of the current mRNA-LNP COVID-19 vaccines.

The stability and quality attributes of liposomes and LNPs have been reviewed by Fan et al. (Fan et al., 2021). LNPs can undergo chemical and physical instability. Chemical instability comprises the degradation of the lipids in the LNPs that are susceptible to hydrolysis and oxidation. Lipid oxidation can occur in unsaturated fatty acid moieties (not present in Comirnaty and mRNA-1273) and with cholesterol, potentially as a result of a hydroperoxide attack, an impurity present in the PEG-group of PEG2000-C-DMG (Jaeger et al., 1994; Wang et al., 2019). Oxidative impurities may also result in oxidation of encapsulated mRNA. The carboxylic ester bonds in lipids, such as DSPC and the ionizable cationic lipids, are susceptible to temperature- and pH-dependent hydrolysis (Fig. 6).

Another key aspect of LNP stability is physical degradation. There are three main types of physical instability that can occur: aggregation, fusion, and leakage of the encapsulated pharmaceutical ingredient. Aggregation of LNPs during storage and fusion of LNPs has been reported (Ayat et al., 2019; Ball et al., 2016). To increase stability on the shelf, LNPs are often formulated with PEG-lipids (Burke et al., 2013; Ryals et al., 2020). The PEG-molecules at the surface prevent the individual LNPs from aggregating. The other type of physical degradation –leakage of the mRNA– mainly affects the stability of the encapsulated product. Of note, encapsulation efficiencies are typically > 90% and release of the RNA payload from LNPs during storage has not been reported (as measured with the RiboGreen test). mRNA that is not encapsulated ('naked mRNA') is hardly taken up by cells; besides, it degrades rapidly and is, therefore, not available for translation.

Hypersensitivity reactions –rarely observed upon intramuscular

injection of the mRNA-LNP COVID-19 vaccines– may be related to the PEG-lipids. Therefore, alternative lipids to prevent aggregate formation have been investigated. Introduction of polysarcosine-modified lipids stabilized lipid-based systems against aggregation while reducing the immunostimulatory response (Nogueira et al., 2020). Additional testing is needed to establish whether such PEG-lipid alternatives improve the mRNA stability (e.g., owing to lack of peroxides).

3.4. Analyzing LNP stability

Analytical methods to monitor the stability of LNPs have been expertly reviewed in the previously mentioned article by Fan et al. and Kim et al. and we refer the interested reader to this literature source (Fan et al., 2021; Kim et al., 2021).

3.5. Which mRNA-LNP component is more unstable: The mRNA, the lipids, or the combination?

To date, several studies have investigated ways to stabilize mRNA and to stabilize LNPs during storage (Ball et al., 2016; Jones et al., 2007). It is, however, interesting to question which of these components is the bottleneck for stability. Is it the mRNA that degrades when the mRNA-LNP formulations are not frozen, are the LNPs causing the problem, or is it the combination of mRNA with the LNPs?

LNP systems entrapping chemically modified and highly stable siRNA molecules (e.g. Onpattro) have significantly longer shelf lives as compared to mRNA-LNP systems. This would suggest that not the LNP, but rather the mRNA is the current stability bottleneck.

To date, there is no research report available in the public domain on the integrity of both mRNA and LNPs in mRNA-LNP formulations. In the few studies in which the effect of storage is investigated, such as the research by Zhang et al. (N.-N. Zhang et al., 2020), long-term effects are not measured. Therefore, we will be looking first at the long-term stability of naked mRNA, with the caveat that this may be different from the stability of mRNA encapsulated in LNPs (see below).

In their review Pascolo et al. remark that aqueous solutions of naked mRNA can be stored at 4 °C for only a few days, provided that the mRNA is protected from degradation by contaminating ribonucleases by an RNase inhibitor (Pascolo, 2008). This seems to be in line with the current view of mRNA instability. The existing body of research on the long-term stability of naked mRNA suggests that mRNA needs to be frozen or dried in order to stay stable for longer periods of time.

In 2009, Roesler et al. show that the translation efficacy of mRNA encoding luciferase begins to decrease after 8 days or 16 days when stored –RNase free– at room temperature as a liquid or in a lyophilized form, respectively. No efforts were made to optimize the formulations in terms of excipients and freeze drying conditions (Fig. 7) (Roesler et al., 2009). Conclusions about the long-term stability at refrigerator

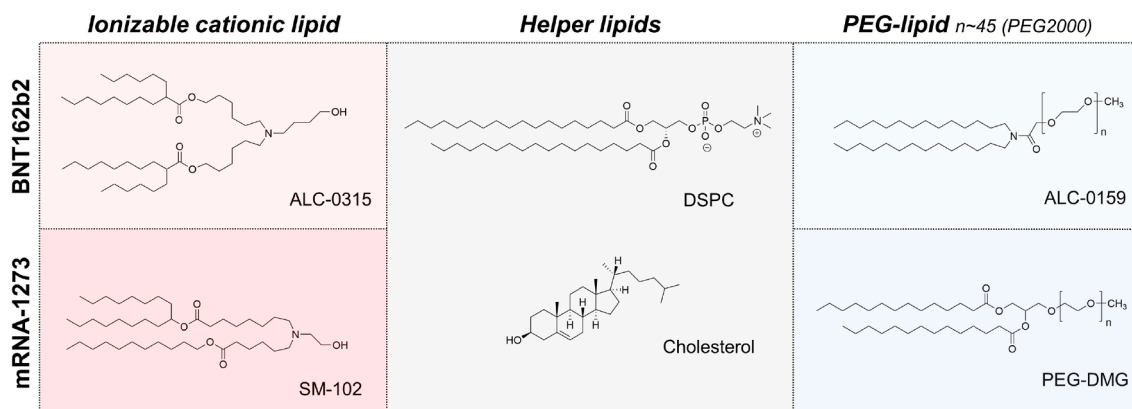


Fig. 6. Lipids used in the mRNA-LNP COVID-19 vaccines BNT162b2 (Comirnaty) and mRNA-1273.

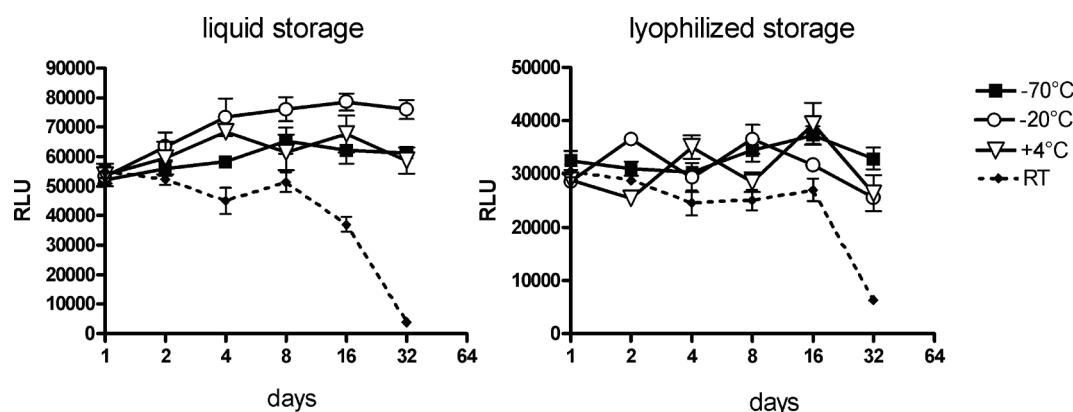


Fig. 7. Stability of mRNA in water analysed by luciferase expression in transfected BHK-21 cells. Courtesy of Roesler et al. (2009).

temperatures can not be drawn from this study, as the stability was only followed for 32 days. There is also information based on theoretical cleavage rate calculations. Wayment-Steele *et al.* predict that mRNA (4000 nt) will have a half-life of 941 days when it is stored at pH 7.4 and 5 °C (Wayment-Steele et al., 2020). They do note that longer mRNA sequences, such as SAMs, are more prone to hydrolysis. Because this is a theoretical calculation that is only based on hydrolytic degradation kinetics, it might underestimate mRNA degradation, e.g., when trace amounts of RNase are present. More research into the stability of mRNA would have to be done to find a definitive answer.

Together, these studies indicate that in an aqueous solution mRNA likely is less stable than LNPs. However, it should be reiterated that results on these two components in isolation could differ from the situation of mRNA encapsulated by LNPs. As discussed in previous sections, mRNA is located inside the LNP core together with an ionizable cationic lipid, cholesterol and water (cf. Fig. 4) (Arteta et al., 2018). This would mean that the mRNA is in an aqueous environment and therefore is susceptible to hydrolysis. The mechanisms of hydrolysis might then be similar to those for mRNA in solution (Brader et al., 2021). However, on the other hand, mRNA inside the LNPs may be coated by the ionizable lipid through hydrophobic, hydrogen-bond and/or electrostatic interactions. In that case the mRNA might be more stable than naked mRNA dissolved in an aqueous medium. Without further studies, it can only be concluded that mRNA instability dictates storage conditions and drives the search for improved, more stable formulations.

3.6. Reasons for different storage conditions

Another interesting aspect of the current mRNA vaccines is that the reported storage temperatures and corresponding 'shelf lives' vary widely: from -80 °C to 2–8 °C and from days to months (Crommelin et al., 2021). Is it possible to identify a difference in the formulation of the mRNA vaccines that could cause this variation? Or, could the difference in storage conditions be related to the limitations of the thermostability testing protocol or a more guarded approach (Schmid, 2017)? This information is important, as insights into the factors that positively affect the stability may be an interesting starting point for the future design of thermostable mRNA vaccines.

Tom Madden, the CEO of Acuitas Therapeutics, stated that the Moderna and Pfizer/BioNTech mRNA vaccines likely have the same stability (Dolgin, 2020). Is it possible that the latter use a more conservative approach to ensure stability? Still, it is quite likely that the Pfizer/BioNTech mRNA-LNP vaccine, that currently has to be stored between -60 to -80 °C was also tested at higher temperatures and under refrigerated conditions as done by CureVac scientists (Stitz et al., 2017). Moreover, the analysis techniques in the stability tests could differ in sensitivity as could the acceptance criteria. Publication of the stability study reports would provide the answers and it would be

interesting to run comparative studies.

4. Opportunities for improving shelf life & storage conditions

When freezing is needed to keep a vaccine stable, distribution, storage and handling by the end-user are highly protocolized and costs increase. For distribution purposes, vaccine stability at refrigerator temperatures, 2–8 °C, would be a desired improvement. In the following section we will focus on research to achieve such storage conditions, as these are seen as a considerable inconvenience for large scale use of mRNA vaccines, such as in the COVID-19 pandemic.

4.1. Excipients

The conclusion from the previous section on the stability of mRNA vaccines is that in order to create more stable mRNA-LNP vaccines, stabilizing the mRNA is the first target. Obviously, any excipient used for mRNA-based vaccines must be RNase free. A review by Muralidhara *et al.* captures a lot of information on the impact of excipients and formulation milieu (Muralidhara et al., 2016).

Some of the excipients proposed by Muralidhara *et al.* are already used in the mRNA vaccines by Moderna and Pfizer/BioNTech. Excipients in the formulations serve as buffers, osmolytes and cryoprotectant or have a dual effect. Moderna, for example, uses a Tris-HCl buffer that would have an additional stabilizing effect on nucleic acid macromolecules as it is also a hydroxyl radical scavenger (EMA, 2021). When selecting these excipients, one should keep in mind that the product may need to be stored at sub-zero temperatures and excipients affect that milieu. The choice of the buffering system and osmolyte is important as the pH may change upon freezing, as has been shown for sodium phosphate buffered systems; a 3.5 pH-units drop occurs upon freezing. Histidine buffers are more 'pH-resistant' upon freezing. But still, the pH may drop 0.5 unit when cooling from 0 °C to -30 °C (Kolhe et al., 2010). And, another example, NaCl (osmolyte)-solutions have a eutectic temperature of -21 °C. Other excipients that could be added are antioxidants, non-reducing free radical scavengers (e.g., ethanol) or metal chelators (Evans et al., 2000). However, the question remains to what extent they indeed ameliorate the stability of mRNA-LNP formulations during storage below or above 0 °C.

pH optimization is also important for mRNA vaccine stability, as the pH influences the hydrolysis rate of mRNA and also LNP stability. Generally, mRNA is most stable in a weakly basic environment. The pH of the Moderna and Pfizer/BioNTech vaccines is between 7 and 8. Wayment-Steele *et al.* make the point that the apparent pH at the surface of the cationic, fully charged lipids could be higher than in the immediate surrounding aqueous medium (Wayment-Steele et al., 2020).

4.2. Lyophilization

As the presence of water initiates degradation reactions in mRNA-LNPs, lyophilization would be a logical step to improve the long-term stability of mRNA-LNP formulations. The head of viral vaccines research at Pfizer, Philip Dormitzer, has already mentioned Pfizer's aspiration to use lyophilization for mRNA-LNP SARS-CoV-2 vaccines (Dolgin, 2020). Moreover, a lyophilized form of a mRNA-based cytomegalovirus vaccine (mRNA-1647) is used in a phase 2 clinical trial. It has a claimed shelf life at 5 °C of ≥ 18 months. However, no details on the formulation and production process can be found in the public domain (Moderna, 2021).

Freeze drying is widely used for live, attenuated virus vaccines (Hansen et al., 2015). It has also already been investigated for naked mRNA formulations, demonstrating its applicability and beneficial effect on mRNA stabilisation. Previous research by Jones *et al.* shows that freeze-dried mRNA formulated with trehalose is stable at 4 °C for up to 10 months (Jones et al., 2007). Lipid nanoparticles can be successfully freeze dried as well. During the freeze-drying process the structures are exposed to stress. Therefore, lyoprotectants that stabilize these colloidal particles should be included in the formulation. Sucrose or trehalose are used for that purpose (Abdelwahed et al., 2006). Thus, the studies with either mRNA or with LNPs suggest that lyophilization could be a possible way to increase the stability of the combination, mRNA-LNP, and could thereby allow for storage at higher temperatures than those currently required. However, lyophilization does have its downsides, as it requires reconstitution before administration and is a relatively expensive, energy- and time-consuming process. On the other hand, keeping the mRNA vaccines (deep)frozen also comes at a cost. Therefore, a logical next step is to investigate whether lyophilization is a viable option for mRNA-LNP formulations.

Shirane *et al.* freeze dried the ethanol-containing siRNA-LNP dispersion obtained immediately after LNP formation and found no difference between the gene knockdown efficiency of the freshly prepared (ethanol removed by ultrafiltration) and the reconstituted freeze-dried formulations *in vivo* (Shirane et al., 2018). These results show promise for the feasibility of lyophilization of mRNA-LNPs, while recognizing the structural differences between siRNA and mRNA.

There is little published data on the lyophilization of mRNA-LNPs, but there is one recent paper by Zhao *et al.* studying mRNA lipid-like nanoparticles (Zhao et al., 2020). They studied the effect of freeze-drying of these nanoparticles that contain an ionizable cationic lipid-like molecule. No details of the -freeze-drying process are provided. Contrary to the data on siRNA-LNPs obtained by Shirane *et al.*, they found that after lyophilization and reconstitution the *in vitro* test showed no loss of activity, but the *in vivo* efficiency was lost. Thus, freeze-drying of mRNA-LNPs might be a more difficult task than previous research suggests. It would be helpful to elucidate the mechanism behind this nullification of *in vivo* efficiency. It could, for example, be that the formulation was suboptimal for freeze-drying or that the lyophilization process itself was flawed. The authors speculate that an alteration in the nanostructure of the mRNA-LNPs may have caused the low *in vivo* efficacy, as such a change could affect properties like the binding to serum proteins, which are absent in the *in vitro* study. Therefore, further improvement of the formulation excipients and freeze-drying conditions might lead to successful lyophilization of mRNA-LNPs.

Another approach, in case lyophilization of the fully prepared mRNA-LNPs complex is problematic, is to lyophilize naked mRNA and combine it with the LNPs shortly before administration. Ball *et al.* successfully followed the opposite approach by reconstituting freeze dried LNPs with siRNA/ethanol solutions (Ball et al., 2016). They correctly pointed out that: 'Unfortunately, the addition of ethanol to reconstitution solutions is often neither convenient nor practical, as dialysis into aqueous buffer would be required before use in animals or in the clinic' If one wishes to avoid freeze drying or organic solvents for the generation of active mRNA-LNPs, one may mix an 'empty' LNP aqueous

suspension with 'fresh' mRNA and find that the mRNA is taken up and active (Leavitt et al., 2020).

Apart from challenges to preserve the integrity of mRNA-LNP through lyophilization, there are other hurdles such as the high energy consumption of the process and other costs, e.g., those related to the necessary, dramatic expansion of the lyophilization capacity worldwide in times of a pandemic. Therefore, it is worthwhile to consider alternative drying techniques. Only one publication could be found on spray drying of mRNA-LNPs where polymers (e.g., Eudragit) were needed as stabilizers for mRNA-LNPs to secure translation efficiency *in vivo* (Karve et al., 2020). Supercritical drying techniques would be another alternative for freeze-drying; they have been shown to be feasible –with their pros and cons– for other macromolecular biotech products, such as proteins (Jovanović et al., 2004).

5. Conclusions and prospects

This review outlines how different aspects of the current mRNA vaccine formulations influence their stability during storage. We conclude that exposure of mRNA to water likely is the main factor for mRNA vaccine instability. An implication of this is that decreasing the exposure to water would be a promising approach for improving mRNA vaccine stability.

The studies on mRNA-LNP structures indicate that the mRNA is located in the core of LNPs together with ionizable cationic lipid and water. This raises important questions about the possible shielding of the mRNA from water. It is, for example, unknown if and how the ionizable cationic lipids in the LNP interact with the mRNA. More work needs to be done to confirm the proposed structure and to understand the consequences. For instance, the pH inside the LNPs has been identified as an important characteristic to study in relation to stability. Another object of study would be to specifically analyze the type(s) of degradation that mRNA molecules undergo in their final formulation and whether sequence adjustment could help to maintain strand integrity. This could then also be coupled to characterization and optimization of the secondary and tertiary structure of mRNA, as there are indications that some folded structures are more stable.

This report is the first comprehensive survey of the factors behind mRNA-LNP vaccine instability. It also points towards solutions to address this instability and thereby may be of assistance to the development of more thermostable mRNA-LNP vaccines, alleviating a major barrier for the distribution of these vaccines.

CRedit authorship contribution statement

Linde Schoenmaker: Conceptualization, Writing - review & editing. **Dominik Witzigmann:** Writing - review & editing. **Jayesh A. Kul-karni:** Writing - review & editing. **Rein Verbeke:** Writing - review & editing. **Gideon Kersten:** Writing - review & editing. **Wim Jiskoot:** Conceptualization, Writing - review & editing. **Daan Crommelin:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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EXHIBIT 9



Time is of the essence to provide
a vaccine against this pandemic virus.

Moderna is proud to be among the many groups working to respond to this continuing global health emergency. This page summarizes key milestones in our work to advance a COVID-19 vaccine.

[View](#) Moderna's standard Informed Consent Form and Authorization To Use and Disclose Protected Health Information for Protocol Number mRNA-1273-P301.

Takeda Pharmaceutical Co., Ltd submitted a New Drug Application to the Government of Japan's Ministry of Health, Labour and Welfare (MHLW) to import and distribute Moderna's vaccine candidate against COVID-19 in Japan.	Mar 05 2021
Moderna completed manufacturing of clinical trial material for its variant-specific vaccine candidate, mRNA-1273.351, against the SARS-CoV-2 variant known as B.1.351 and shipped doses to the NIH for a Phase 1 clinical trial that will be led and funded by NIAID.	Feb 24 2021
Moderna announced new capital investments to increase capacity at its owned and partnered manufacturing facilities, which it expects will increase global 2022 capacity to approximately 1.4 billion doses of its COVID-19 vaccine, assuming a 100 µg dose.	
Results from in vitro neutralization studies of sera from individuals vaccinated with Moderna COVID-19 Vaccine showing activity against emerging strains of SARS-CoV-2.	Jan 25 2021
The first participant was dosed in the Phase 1/2 study of Moderna's vaccine candidate against COVID-19 in Japan, led by Takeda Pharmaceutical Co., Ltd.	Jan 21 2021
Interim safety and primary efficacy results from the Phase 3 COVE study of the Moderna COVID-19 Vaccine were published in the New England Journal of Medicine .	Dec 31 2020
The U.S. Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) voted to recommend the use of the Moderna COVID-19 Vaccine in people 18 years of age and older under the Emergency Use Authorization (EUA) issued by the U.S. FDA.	Dec 19 2020
The FDA authorized the emergency use of mRNA-1273 in individuals 18 years of age or older	Dec 18 2020
The U.S. FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommended that the FDA grant an Emergency Use Authorization (EUA) for the Company's COVID-19 vaccine candidate	Dec 17 2020
The first adolescent participants were dosed in the Phase 2/3 study of mRNA-1273.	Dec 10 2020
Moderna announced the primary efficacy analysis of the Phase 3 COVE study and filed for an Emergency Use Authorization with the U.S. FDA.	Nov 30 2020
mRNA-1273 met its primary efficacy endpoint in the first interim analysis of the Phase 3 COVE study.	Nov 16 2020
Moderna announced a longer shelf life for mRNA-1273 at refrigerated temperatures .	
Moderna completed enrollment of the Phase 3 COVE Study	Oct 22 2020
View the demographic data for the Phase 3 COVE Study	



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Interim results from the older adult age cohorts (ages 56-70 and ages 71+) in the Phase 1 study of mRNA-1273 published in <i>The New England Journal of Medicine</i>	Sep 29 2020
Moderna signed a pledge to continue to make the safety and well-being of vaccinated individuals the top priority in development of the first COVID-19 vaccines.	Sep 08 2020
Moderna announced a supply agreement with the U.S. government for an initial 100 million doses of mRNA-1273.	Aug 11 2020
Non-human primate preclinical viral challenge study of mRNA-1273 published in <i>The New England Journal of Medicine</i>	Jul 28 2020
The Phase 3 study of mRNA-1273 being conducted in collaboration with the NIH and BARDA begins	Jul 27 2020
BARDA expands agreement to support larger Phase 3 program for mRNA-1273	Jul 26 2020
Interim results from the NIH-led Phase 1 study of mRNA-1273 published in <i>The New England Journal of Medicine</i>	Jul 14 2020
Moderna completed enrollment of its Phase 2 study of mRNA-1273.	Jul 08 2020
The cohorts of older adults and elderly adults in NIH-led Phase 1 study of mRNA-1273 completed enrollment .	
Moderna and Catalent announced a collaboration for fill-finish manufacturing of mRNA-1273.	Jun 25 2020
The cohort of younger adults (n=300) and the sentinel group of older adults (n=50) in Moderna's Phase 2 study of mRNA-1273 completed enrollment .	Jun 11 2020
The first participants in each age cohort were dosed in Moderna's Phase 2 study of mRNA-1273.	May 29 2020
Moderna announced positive interim Phase 1 data for mRNA-1273.	May 18 2020
Moderna received FDA Fast Track designation for mRNA-1273.	May 12 2020
Moderna reported that Anthony S. Fauci, M.D., Director of NIAID, participated in an interview with <i>National Geographic</i> , which described his assessment of the results of certain preclinical testing related to the ongoing Phase 1 clinical study of mRNA-1273.	May 06 2020
Moderna and Lonza announced a worldwide strategic collaboration with the goal to enable manufacturing of up to 1 billion doses of mRNA-1273 per year.	May 01 2020
Moderna submitted an IND to the U.S. FDA for Phase 2 study of mRNA-1273.	Apr 27 2020
BARDA awarded Moderna up to \$483 million to accelerate development of mRNA-1273 to enable large-scale production in 2020 for pandemic response.	Apr 16 2020
The NIH-led Phase 1 study of mRNA-1273 completed enrollment of three dose cohorts (25 µg, 100 µg and 250 µg) and expanded to an additional six cohorts: three cohorts of older adults (ages 56 -70) and three cohorts of elderly adults (age 71 and above).	
The NIH announced that Emory University in Atlanta would begin enrolling healthy adult volunteers ages 18 to 55 years in the NIH-led Phase 1 study of mRNA-1273.	Mar 27 2020
While a commercially-available vaccine is not likely to be available for at least 12-18 months, Moderna reported it is possible that under emergency use, a vaccine could be available to some people, possibly including healthcare professionals, in the fall of 2020. ¹	Mar 23 2020
Moderna confirmed that it is scaling up manufacturing capacity toward the production of millions of doses per month, in the potential form of individual or multi-dose vials. ²	



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The NIH **announced** that the first participant in its Phase 1 study of mRNA-1273 was dosed, a total of 63 days from sequence selection to first human dosing.

Mar 16
2020

The FDA completed its review of the IND application filed by the NIH for mRNA-1273 and allowed the study to proceed to clinical trials.

Mar 04
2020

Moderna **shipped** the first clinical batch of mRNA-1273 to the NIH for use in their Phase 1 clinical study.

Feb 24
2020

The first clinical batch of mRNA-1273 was **completed**, a total of 25 days from sequence selection to vaccine manufacture. The batch then proceeded to analytical testing for release.

Feb 07
2020

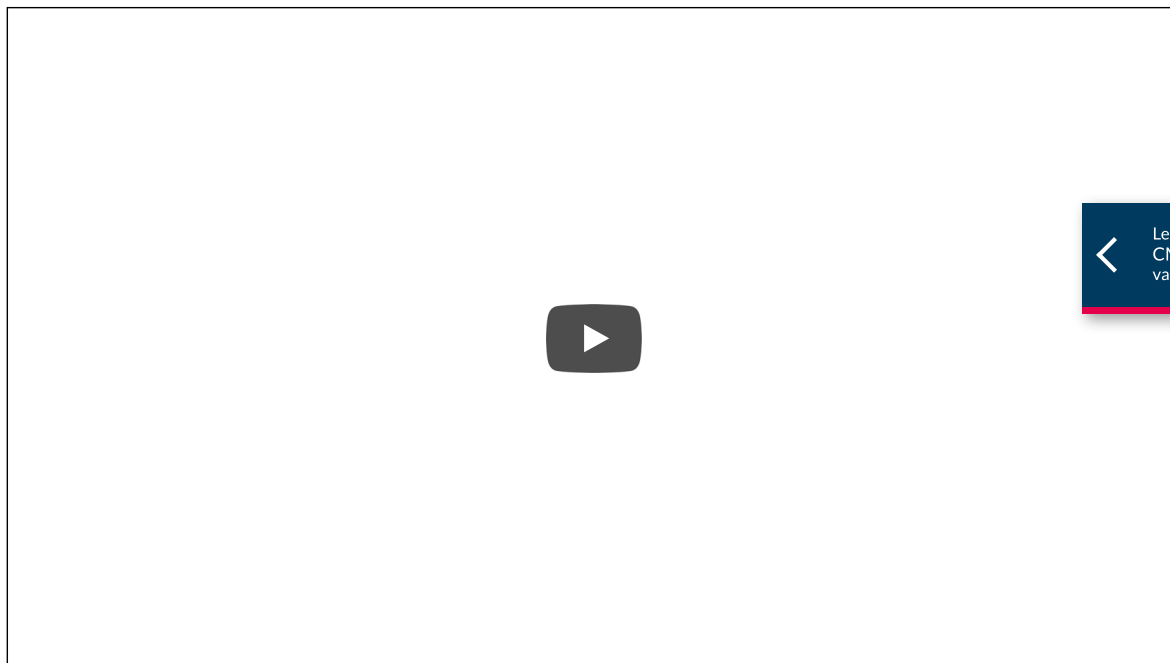
The NIH and Moderna's infectious disease research team finalized the sequence for mRNA-1273. Moderna mobilized toward clinical manufacture.

Jan 13
2020

NIAID, part of NIH, disclosed their intent to run a Phase 1 study using mRNA-1273 in response to the coronavirus threat. Manufacture of this batch was funded by the Coalition for Epidemic Preparedness Innovations (CEPI).

Chinese authorities shared the genetic sequence of the novel coronavirus.

Jan 11
2020



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About mRNA-1273, Moderna's Vaccine Candidate Against COVID-19

Moderna's Ten Years of Research

Since 2010, Moderna has focused on building our mRNA technology platform by leveraging the role mRNA plays in instructing cells to create proteins. Our platform produces mRNA that can be delivered to cells without provoking an immune response against the mRNA itself. Moderna is using this platform to pursue mRNA medicines for a broad spectrum of diseases.

Before there was ever a COVID-19 pandemic, our ten years of research and clinical trials taught us valuable lessons about designing both mRNA therapeutics and mRNA vaccines. This includes, in particular, how to manufacture and formulate mRNA that can produce the targeted proteins – the spike protein, in the case of coronaviruses like the SARS-CoV-2 virus – in the body. Clinical trials of our mRNA vaccine candidates against a variety of viruses have repeatedly demonstrated that they induce the desired immune response.

By the time of the COVID-19 pandemic, we had already been working for years on vaccines for infectious diseases, including on other coronaviruses and their spike proteins. As part of our mRNA technology platform, we had also already developed an mRNA delivery system that was specifically designed for vaccines.

Once the COVID-19 pandemic struck, we were well positioned to adapt our existing mRNA technology to try to address the global public health crisis. We worked closely with the NIH and other government and non-government partners to design and implement a robust COVID-19 vaccine clinical trial program that prioritized safety. Our speed in developing the Moderna COVID-19 vaccine was ultimately a product of our many years of research and investment in mRNA vaccines.

Related Resources



Advantages of mRNA Vaccines



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Moderna's Research Engine



Careers at Moderna

¹ Any emergency use would be subject to authorization by the appropriate regulatory agencies, based on the emergence of clinical data for mRNA-1273 that would support use of the vaccine prior to licensure.

² As has previously been disclosed, the ability of the Company to make millions of doses per month is contingent on investments in the scale up and further buildout of the Company's existing manufacturing infrastructure.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including the Company's development of a potential vaccine against the novel Coronavirus, the conduct and timing of the Phase I study of mRNA-1273, the plan and timing of a potential Phase 2 and any subsequent trials of mRNA-1273, and potential manufacturing capabilities. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this summary and FAQ are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: the fact that there has never been a commercial product utilizing mRNA technology approved for use; the fact that the rapid response technology in use by Moderna is still being developed and implemented; and those other risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this summary and FAQ in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.



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Authorized Use

Moderna COVID-19 Vaccine is **authorized** for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. Moderna COVID-19 Vaccine is investigational and not approved by FDA.

IMPORTANT SAFETY INFORMATION

- Do not administer the Moderna COVID-19 Vaccine to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the Moderna COVID-19 Vaccine.
- Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the Moderna COVID-19 Vaccine. Monitor Moderna COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (<https://www.cdc.gov/vaccines/covid-19/>).
- Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished response to the Moderna COVID-19 Vaccine.
- The Moderna COVID-19 Vaccine may not protect all vaccine recipients.

- Adverse reactions reported in a clinical trial following administration of the Moderna COVID-19 Vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site. Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Moderna COVID-19 Vaccine.
- Available data on Moderna COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. Data are not available to assess the effects of Moderna COVID-19 Vaccine on the breastfed infant or on milk production/excretion.
- There are no data available on the interchangeability of the Moderna COVID-19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Moderna COVID-19 Vaccine should receive a second dose of Moderna COVID-19 Vaccine to complete the vaccination series.
- Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Moderna COVID-19 Vaccine.
- Vaccination providers must complete and submit reports to VAERS online at <https://vaers.hhs.gov/reportevent.html>. For further assistance with reporting to VAERS, call 1-800-822-7967. The reports should include the words "Moderna COVID-19 Vaccine EUA" in the description section of the report.

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EXHIBIT 10



Moderna Announces IND Submitted to U.S. FDA for Phase 2 Study of mRNA Vaccine (mRNA-1273) Against Novel Coronavirus

April 27, 2020

600 participant Phase 2 study to begin upon IND acceptance and safety data from ongoing NIH-led Phase 1 study

Planning underway for Phase 3 study; study expected to begin in the fall of 2020

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 27, 2020-- Moderna, Inc., (Nasdaq: MRNA) a clinical stage biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that it has submitted an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) for the company's mRNA vaccine candidate (mRNA-1273) against the novel coronavirus (SARS-CoV-2) to evaluate mRNA-1273 in Phase 2 and late-stage studies if supported by safety data from the Phase 1 study led by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

Moderna has received initial feedback from the FDA on the design of the planned Phase 2 study, which is expected to begin in the second quarter of 2020. This study will evaluate the safety, reactogenicity and immunogenicity of two vaccinations of mRNA-1273 given 28 days apart. Each subject will be assigned to receive placebo, a 50 µg or a 250 µg dose at both vaccinations. The company intends to enroll 600 healthy participants across two cohorts of adults ages 18-55 years (n=300) and older adults ages 55 years and above (n=300). Participants will be followed through 12 months after the second vaccination.

"Submitting this IND is an important next step in the clinical development of our mRNA vaccine against SARS-CoV-2, and we are moving rapidly to potentially address this global health emergency," said Tal Zaks, M.D., Ph.D., Chief Medical Officer at Moderna. "We look forward to launching this Phase 2 study as soon as possible, which will provide important information about the safety, reactogenicity and immunogenicity of mRNA-1273."

Subject to data from the Phase 1 and Phase 2 studies and discussions with regulators, a Phase 3 study could begin in the fall of 2020. [Funding](#) from the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services, supported the planning for these studies and also will support the late-stage clinical development programs, as well as the scale-up of mRNA-1273 manufacturing.

"Safe, effective vaccines are critical to ending this pandemic and preventing future outbreaks of SARS-COV-2," said BARDA Acting Director Gary Disbrow, Ph.D. "The next steps announced today for this particular vaccine highlight the value of collaboration among government agencies including BARDA and NIAID, and the private sector, to move vaccines and other medical countermeasures forward as rapidly as possible."

About the NIAID-led Phase 1 Study

An open-label Phase 1 study of mRNA-1273 is being conducted by the National Institute of Allergy and Infectious Diseases under its own Investigational New Drug (IND) application. The Phase 1 study, which began on March 16, 2020, completed enrollment of 45 healthy adult volunteers ages 18 to 55 years in the original three dose cohorts (25 µg, 100 µg and 250 µg). The study is [enrolling](#) an additional six cohorts: three cohorts of older adults (ages 56-70) and three cohorts of elderly adults (ages 71 and above). Data from the original cohort of healthy adult volunteers ages 18 to 55 years will be reported once available.

About mRNA-1273

mRNA-1273 is an mRNA vaccine against SARS-CoV-2 encoding for a prefusion stabilized form of the Spike (S) protein, which was selected by Moderna in collaboration with investigators from Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), a part of the NIH. The first clinical batch, which was funded by the Coalition for Epidemic Preparedness Innovations, was completed on February 7, 2020 and underwent analytical testing; it was shipped to NIH on February 24, 42 days from sequence selection. The first participant in the NIAID-led Phase 1 study of mRNA-1273 was dosed on March 16, 63 days from sequence selection to Phase 1 study dosing. A summary of the company's work to date on SARS-CoV-2 can be found [here](#).

About Moderna's Prophylactic Vaccines Modality

Moderna scientists designed the company's prophylactic vaccines modality to prevent infectious diseases. More than 1,400 participants have been enrolled in Moderna's infectious disease vaccine clinical studies under health authorities in the U.S., Europe and Australia. Clinical data demonstrate that Moderna's proprietary vaccine technology has been generally well-tolerated and can elicit durable immune responses to viral antigens. Based on clinical experience across Phase 1 studies, the company designated prophylactic vaccines a core modality and is working to accelerate the development of its vaccine pipeline.

The potential advantages of an mRNA approach to prophylactic vaccines include the ability to combine multiple mRNAs into a single vaccine, rapid discovery to respond to emerging pandemic threats and manufacturing agility derived from the platform nature of mRNA vaccine design and production. Moderna has built a fully integrated manufacturing plant which enables the promise of the technology platform.

Moderna currently has [nine development candidates](#) in its prophylactic vaccines modality, including:

Vaccines against respiratory infections

- Respiratory syncytial virus (RSV) vaccine for older adults (mRNA-1777 and mRNA-1172 or V172 with Merck)
- RSV vaccine for young children (mRNA-1345)
- Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) vaccine (mRNA-1653)

- Novel coronavirus (SARS-CoV-2) vaccine (mRNA-1273)
- Influenza H7N9 (mRNA-1851)

Vaccines against infections transmitted from mother to baby

- Cytomegalovirus (CMV) vaccine (mRNA-1647)
- Zika vaccine (mRNA-1893 with BARDA)

Vaccines against highly prevalent viral infections

- Epstein-Barr virus (EBV) vaccine (mRNA-1189)

To date, Moderna has demonstrated positive Phase 1 data readouts for seven prophylactic vaccines (H10N8, H7N9, RSV, chikungunya virus, hMPV/PIV3, CMV and Zika). Moderna's CMV vaccine is currently in a Phase 2 dose-confirmation study. Moderna's investigational Zika vaccine (mRNA-1893), currently in a Phase 1 study, was granted FDA Fast Track designation in August 2019.

About Moderna

Moderna is advancing messenger RNA (mRNA) science to create a new class of transformative medicines for patients. mRNA medicines are designed to direct the body's cells to produce intracellular, membrane or secreted proteins that can have a therapeutic or preventive benefit and have the potential to address a broad spectrum of diseases. The company's platform builds on continuous advances in basic and applied mRNA science, delivery technology and manufacturing, providing Moderna the capability to pursue in parallel a robust pipeline of new development candidates. Moderna is developing therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases and cardiovascular diseases, independently and with strategic collaborators.

Headquartered in Cambridge, Mass., Moderna currently has strategic alliances for development programs with AstraZeneca PLC and Merck & Co., Inc., as well as the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense, and the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS). Moderna has been ranked in the top ten of *Science's* list of top biopharma industry employers for the past five years. To learn more, visit www.modernatx.com.

Forward Looking Statement

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding the company's development of a potential vaccine against the novel coronavirus, the parameters and timing of the planned Phase 2 study of mRNA-1273, the potential timing of a Phase 3 study of mRNA-1273, BARDA funding for clinical studies and manufacturing activities and timing of data from the Phase 1 study of mRNA-1273. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: the fact that there has never been a commercial product utilizing mRNA technology approved for use; the fact that the rapid response technology in use by Moderna is still being developed and implemented; the fact that the safety and efficacy of mRNA-1273 has not yet been established; potential adverse impacts due to the global COVID-19 pandemic such as delays in regulatory review, manufacturing and supply chain interruptions, adverse effects on healthcare systems and disruption of the global economy; and those other risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

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Source: Moderna, Inc.

EXHIBIT 11



Moderna Announces Supply Agreement with U.S. Government for Initial 100 Million Doses of mRNA Vaccine Against COVID-19 (mRNA-1273)

August 11, 2020

New U.S. government award up to \$1.525 billion for 100 million doses

Option granted to U.S. government to purchase up to an additional 400 million doses

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 11, 2020-- Moderna, Inc., (Nasdaq: MRNA) a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that the U.S. government has secured 100 million doses of mRNA-1273 as part of the U.S. government's goal of securing early access to safe and effective COVID-19 vaccines for the American people.

Today's award of up to \$1.525 billion is for the manufacturing and delivery of 100 million doses of mRNA-1273 including incentive payments for timely delivery of the product. With the previous award of up to \$955 million from BARDA for the development of mRNA-1273 to licensure, today's announcement brings the U.S. government commitments for early access to mRNA-1273 to up to \$2.48 billion. Under the terms of the agreement, the U.S. government, as a part of Operation Warp Speed, will also have the option to purchase up to an additional 400 million doses of mRNA-1273 from Moderna. The U.S. government has announced that consistent with its commitment to free access to COVID-19 vaccines, Americans will receive mRNA-1273 at no cost for the vaccine itself. As is customary with government-purchased vaccines, healthcare professionals could charge for the cost of administering the vaccine.

"We appreciate the confidence of the U.S. government in our mRNA vaccine platform and the continued support," said Stéphane Bancel, Moderna's Chief Executive Officer. "We are advancing the clinical development of mRNA-1273 with the ongoing Phase 3 study being conducted in collaboration with NIAID and BARDA. In parallel, we are scaling up our manufacturing capability with our strategic partners, Lonza, Catalent and Rovi, to address this global health emergency with a safe and effective vaccine."

"For Operation Warp Speed, we are assembling a broad portfolio of vaccines to increase the odds that we will have at least one safe, effective vaccine as soon as the end of this year," said HHS Secretary Alex Azar. "With this latest investment, we will have supported the vaccine candidate developed by Moderna in partnership with the NIH all the way from early development through clinical trials and now manufacturing, with the potential to bring millions of safe and effective doses to the American people."

Over the past nine years, Moderna has invested in creating and developing a novel platform for designing and manufacturing a new class of mRNA-based vaccines. The investments in this proprietary platform have enabled Moderna to expeditiously create, manufacture and clinically develop mRNA-1273 to potentially address the current COVID-19 pandemic. A summary of the company's work to date on COVID-19 can be found [here](#).

The Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS), supported the research and development of mRNA-1273 with \$955 million in federal funding under Contract no. 75A50120C00034. BARDA is reimbursing Moderna for 100 percent of the allowable costs incurred by the company for conducting the program described in the BARDA contract. The U.S. government is providing up to \$1.525 billion in funding for the supply of mRNA-1273 under U.S. Department of Defense Contract No. W911QY-20-C-0100.

About mRNA-1273

mRNA-1273 is an mRNA vaccine against COVID-19 encoding for a [prefusion stabilized](#) form of the Spike (S) protein, which was co-developed by Moderna and investigators from the National Institute of Allergy and Infectious Disease's (NIAID) Vaccine Research Center. The first clinical batch, which was funded by the Coalition for Epidemic Preparedness Innovations, was completed on February 7, 2020 and underwent analytical testing; it was shipped to the National Institutes of Health (NIH) on February 24, 42 days from sequence selection. The first participant in the NIAID-led Phase 1 study of mRNA-1273 was dosed on March 16, 63 days from sequence selection to Phase 1 study dosing. On May 12, the FDA granted mRNA-1273 Fast Track designation. On May 29, the first participants in each age cohort: healthy adults ages 18-55 years (n=300) and older adults ages 55 years and above (n=300) were dosed in the Phase 2 study of mRNA-1273. On July 8, the [Phase 2 study](#) completed enrollment.

The Phase 3 COVE study of mRNA-1273, being conducted in collaboration with the NIH and BARDA, began on July 27; enrollment is on track to complete in September. Results from a non-human primate preclinical viral challenge study evaluating mRNA-1273 were recently [published](#) in *The New England Journal of Medicine*. On July 14, an interim analysis of the original cohorts in the NIH-led Phase 1 study of mRNA-1273 was [published](#) in *The New England Journal of Medicine*.

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- COVID-19 vaccine (mRNA-1273)
- Influenza H7N9 vaccine (mRNA-1851)

Vaccines against infections transmitted from mother to baby

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- Zika vaccine (mRNA-1893 with BARDA)

Vaccines against highly prevalent viral infections

- Epstein-Barr virus (EBV) vaccine (mRNA-1189)

To date, Moderna has demonstrated positive Phase 1 data readouts for eight prophylactic vaccines (H10N8, H7N9, RSV, chikungunya virus, hMPV/PIV3, CMV, Zika and COVID-19). Moderna's CMV vaccine is currently in a Phase 2 dose-confirmation study. Moderna's investigational Zika vaccine (mRNA-1893), currently in a Phase 1 study, was granted FDA Fast Track designation in August 2019.

About Moderna

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Headquartered in Cambridge, Mass., Moderna currently has strategic alliances for development programs with AstraZeneca PLC and Merck & Co., Inc., as well as the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense; the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS) and the Coalition for Epidemic Preparedness Innovations (CEPI). Moderna has been named a top biopharmaceutical employer by *Science* for the past five years. To learn more, visit www.modernatx.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended including, but not limited to, statements concerning terms of the Company's collaboration with the U.S. Government and the timing of enrollment in the Phase 3 study of mRNA-1273 and the cost of the vaccine to Americans. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: the ability to manufacture and deliver doses at the scale required by the agreement with the U.S. Government; the lack of a guarantee the U.S. Government will exercise its option to purchase additional doses; preclinical and clinical development is lengthy and uncertain, especially for a new class of medicines such as mRNA, and therefore our preclinical programs or development candidates may be delayed, terminated, or may never advance to or in the clinic; no commercial product using mRNA technology has been approved, and may never be approved; mRNA drug development has substantial clinical development and regulatory risks due to the novel and unprecedented nature of this new class of medicines; despite having ongoing interactions with the FDA or other regulatory agencies, the FDA or such other regulatory agencies may not agree with the Company's regulatory approval strategies, components of our filings, such as clinical trial designs, conduct and methodologies, or the sufficiency of data submitted; the fact that the rapid response technology in use by Moderna is still being developed and implemented; the fact that the safety and efficacy of mRNA-1273 has not yet been established; potential adverse impacts due to the global COVID-19 pandemic such as delays in clinical trials, preclinical work, overall operations, regulatory review, manufacturing and supply chain interruptions, adverse effects on healthcare systems and disruption of the global economy; and those risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

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EXHIBIT 12



Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization

November 30, 2020

Primary efficacy analysis of the Phase 3 COVE study of mRNA-1273 involving 30,000 participants included 196 cases of COVID-19, of which 30 cases were severe

Vaccine efficacy against COVID-19 was 94.1%; vaccine efficacy against severe COVID-19 was 100%

mRNA-1273 continues to be generally well tolerated; no serious safety concerns identified to date

Phase 3 COVE Study has exceeded 2 months of median follow-up post vaccination as required by the U.S. FDA for Emergency Use Authorization (EUA)

Moderna plans today to request EUA from the U.S. FDA, to apply for a conditional marketing authorization with the European Medicines Agency (EMA) and to progress with the rolling reviews, which have already been initiated with international regulatory agencies

FDA has told Company to expect VRBPAC meeting for mRNA-1273 likely on December 17, 2020

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 30, 2020-- [Moderna, Inc.](#) (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that the primary efficacy analysis of the Phase 3 study of mRNA-1273 conducted on 196 cases confirms the high efficacy observed at the first interim analysis. The data analysis indicates a vaccine efficacy of 94.1%. Safety data continue to accrue and the study continues to be monitored by an independent, NIH-appointed Data Safety Monitoring Board (DSMB). The Company also announced that today, Moderna plans to request an Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration (FDA) and conditional approval from the European Medicines Agency (EMA). The Phase 3 study, known as the COVE study, enrolled more than 30,000 participants in the U.S. and is being conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services.

The primary endpoint of the Phase 3 COVE study is based on the analysis of COVID-19 cases confirmed and adjudicated starting two weeks following the second dose of vaccine. Vaccine efficacy has been demonstrated at the first interim analysis with a total of 95 cases based on the pre-specified success criterion on efficacy. Today's primary analysis was based on 196 cases, of which 185 cases of COVID-19 were observed in the placebo group versus 11 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.1%. A secondary endpoint analyzed severe cases of COVID-19 and included 30 severe cases (as defined in the study [protocol](#)) in this analysis. All 30 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group. There was one COVID-19-related death in the study to date, which occurred in the placebo group.

Efficacy was consistent across age, race and ethnicity, and gender demographics. The 196 COVID-19 cases included 33 older adults (ages 65+) and 42 participants identifying as being from diverse communities (including 29 Hispanic or LatinX, 6 Black or African Americans, 4 Asian Americans and 3 multiracial participants).

The safety profile of the Phase 3 study of mRNA-1273 was [previously described](#) on November 16. A continuous review of safety data is ongoing and no new serious safety concerns have been identified by the Company. Based on prior analysis, the most common solicited adverse reactions included injection site pain, fatigue, myalgia, arthralgia, headache, and erythema/redness at the injection site. Solicited adverse reactions increased in frequency and severity in the mRNA-1273 group after the second dose.

The Company will submit data from the Phase 3 COVE study to a peer-reviewed publication.

"This positive primary analysis confirms the ability of our vaccine to prevent COVID-19 disease with 94.1% efficacy and importantly, the ability to prevent severe COVID-19 disease. We believe that our vaccine will provide a new and powerful tool that may change the course of this pandemic and help prevent severe disease, hospitalizations and death," said Stéphane Bancel, Chief Executive Officer of Moderna. "I want to thank the thousands of participants in our Phase 1, Phase 2 and Phase 3 studies, as well as the staff at clinical trial sites who have been on the front lines of the fight against the virus. I would again like to thank our partners at NIH, NIAID, BARDA and Operation Warp Speed who have helped us advance the clinical development of mRNA-1273. Finally, I want to thank the Moderna team and our suppliers and partners for their tireless work on the research, development and manufacturing of our vaccine. We will file today for an Emergency Use Authorization from the FDA and continue forging ahead with the rolling reviews that have already been initiated with several regulatory agencies around the globe."

Today, Moderna will submit for an EUA with the U.S. FDA and an application for Conditional Marketing Authorization (CMA) with the European Medicines Agency. The Company has already initiated the rolling review process with the EMA, Health Canada, SwissMedic, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), Ministry of Health in Israel, and Health Sciences Authority in Singapore and intends to seek Prequalification (PQ) and/or Emergency Use Listing (EUL) with the World Health Organization (WHO).

Additionally, Moderna announced that the FDA's [Vaccines and Related Biological Products Advisory Committee](#) (VRBPAC) meeting to review the safety and efficacy data package for mRNA-1273 will likely be scheduled for Thursday, December 17. The Company expects that the U.S. Centers for Disease Control and Prevention (CDC) [Advisory Committee on Immunization Practices](#) (ACIP) will make a recommendation on immunization priorities. The Company anticipates that the shipping of mRNA-1273 to designated distribution points throughout the U.S. will occur shortly after an Emergency Use Authorization is granted.

Moderna is working with the U.S. CDC, Operation Warp Speed and McKesson (NYSE: MCK), a COVID-19 vaccine distributor contracted by the U.S.

government, as well as global stakeholders to be prepared for distribution of mRNA-1273, in the event that it receives an EUA and similar global authorizations and approvals. By the end of 2020, the Company expects to have approximately 20 million doses of mRNA-1273 available in the U.S. The Company remains on track to manufacture 500 million to 1 billion doses globally in 2021. On November 10, the American Medical Association (AMA) issued a [Current Procedural Terminology \(CPT\) code](#) to report vaccination with mRNA-1273 (code: 91301). Moderna [recently announced](#) further progress towards ensuring the distribution, storage and handling of the vaccine can be done using existing infrastructure.

To learn more about Moderna's work on mRNA-1273, visit www.modernatx.com/COVID19.

About the Phase 3 COVE Study

The Phase 3 COVE trial is a randomized, 1:1 placebo-controlled study testing mRNA-1273 at the 100 µg dose level in 30,000 participants in the U.S., ages 18 and older. The primary endpoint is the prevention of symptomatic COVID-19 disease. Key secondary endpoints include prevention of severe COVID-19 disease and prevention of infection by SARS-CoV-2. The trial will continue to accrue additional data relevant to safety and efficacy even after an EUA is submitted. The final estimates of vaccine efficacy for both primary and secondary endpoints will depend on the totality of data that will accumulate to inform the final analysis. Moderna worked closely with BARDA and the NIH, including NIAID's COVID-19 Prevention Network ([CoVPN](#)), to conduct the Phase 3 COVE study under Operation Warp Speed. Moderna's partner PPD (Nasdaq: [PPD](#)), a leading global contract research organization providing comprehensive, integrated drug development, laboratory and lifecycle management services, has also been essential to the successful execution of the COVE study.

The Phase 3 COVE study was designed in collaboration with the FDA and NIH to evaluate Americans at risk of severe COVID-19 disease and [completed enrollment](#) of more than 30,000 participants ages 18 and older in the U.S. on October 22, including those at high risk of severe complications of COVID-19 disease. The COVE study includes more than 7,000 Americans over the age of 65. It also includes more than 5,000 Americans who are under the age of 65 but have high-risk chronic diseases that put them at increased risk of severe COVID-19, such as diabetes, severe obesity and cardiac disease. These medically high-risk groups represent 42% of the total participants in the Phase 3 COVE study. The study also included communities that have historically been under-represented in clinical research and have been disproportionately impacted by COVID-19. The study includes more than 11,000 participants from communities of color, representing 37% of the study population, which is similar to the diversity of the U.S. at large. This includes more than 6,000 participants who identify as Hispanic or LatinX, and more than 3,000 participants who identify as Black or African American.

About mRNA-1273

mRNA-1273 is an mRNA vaccine against COVID-19 encoding for a [prefusion stabilized](#) form of the Spike (S) protein, which was co-developed by Moderna and investigators from NIAID's Vaccine Research Center. The first clinical batch, which was funded by the Coalition for Epidemic Preparedness Innovations, was completed on February 7, 2020 and underwent analytical testing; it was shipped to the NIH on February 24, 42 days from sequence selection. The first participant in the NIAID-led Phase 1 study of mRNA-1273 was dosed on March 16, 63 days from sequence selection to Phase 1 study dosing. On May 12, the FDA granted mRNA-1273 Fast Track designation. On May 29, the first participants in each age cohort: adults ages 18-55 years (n=300) and older adults ages 55 years and above (n=300) were dosed in the Phase 2 study of mRNA-1273. On July 8, the [Phase 2 study](#) completed enrollment.

Results from the second interim analysis of the NIH-led Phase 1 study of mRNA-1273 in the 56-70 and 71+ age groups were [published](#) on September 29 in *The New England Journal of Medicine*. On July 28, results from a non-human primate preclinical viral challenge study evaluating mRNA-1273 were [published](#) in *The New England Journal of Medicine*. On July 14, an interim analysis of the original cohorts in the NIH-led Phase 1 study of mRNA-1273 was [published](#) in *The New England Journal of Medicine*. mRNA-1273 currently is not approved for use by any regulatory body.

BARDA is supporting the continued research and development of mRNA-1273 with \$955 million in federal funding under Contract no. 75A50120C00034. BARDA is reimbursing Moderna for 100 percent of the allowable costs incurred by the Company for conducting the program described in the BARDA contract. The U.S. government has agreed to provide up to \$1.525 billion to purchase supply of mRNA-1273 under U.S. Department of Defense Contract No. W911QY-20-C-0100.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding the Company's development of a potential vaccine (mRNA-1273) against the novel coronavirus, mRNA-1273's efficacy and its ability to prevent infection or mitigate symptoms of COVID-19, the safety profile for mRNA-1273, the Company's plans to seek regulatory approval for the use of mRNA-1273 in the U.S. and other jurisdictions, the Company's anticipated production of mRNA-1273, and the timing of the initial shipments of mRNA-1273. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: the fact that there has never been a commercial product utilizing mRNA technology approved for use; the fact that the rapid response technology in use by Moderna is still being developed and implemented; the safety, tolerability and efficacy profile of mRNA-1273 observed to date may change adversely in ongoing analyses of trial data or subsequent to commercialization; despite having ongoing interactions with the FDA or other regulatory agencies, the FDA or such other regulatory agencies may not agree with the Company's regulatory approval strategies, components of our filings, such as clinical trial designs, conduct and methodologies, or the sufficiency of data submitted; Moderna may encounter delays in meeting manufacturing or supply timelines or disruptions in its distribution plans for mRNA-1273; whether and when any biologics license applications and/or emergency use authorization applications may be filed and ultimately approved by regulatory authorities; potential adverse impacts due to the global COVID-19 pandemic such as delays in regulatory review, manufacturing and clinical trials, supply chain interruptions, adverse effects on healthcare systems and disruption of the global economy; and those other risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

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Source: Moderna, Inc.

EXHIBIT 13

FDA NEWS RELEASE

FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine

Action Follows Thorough Evaluation of Available Safety, Effectiveness, and Manufacturing Quality Information by FDA Career Scientists, Input from Independent Experts

For Immediate Release:

December 18, 2020

[Español \(/news-events/press-announcements/la-fda-toma-medidas-adicionales-en-la-lucha-contra-el-covid-19-al-emitir-autorizacion-de-uso-de\)](#)

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the second vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergency use authorization allows the Moderna COVID-19 Vaccine to be distributed in the U.S. for use in individuals 18 years of age and older.

“With the availability of two vaccines now for the prevention of COVID-19, the FDA has taken another crucial step in the fight against this global pandemic that is causing vast numbers of hospitalizations and deaths in the United States each day,” said FDA Commissioner Stephen M. Hahn, M.D. “Through the FDA’s open and transparent scientific review process, two COVID-19 vaccines have been authorized in an expedited timeframe while adhering to the rigorous standards for safety, effectiveness, and manufacturing quality needed to support emergency use authorization that the American people have come to expect from the FDA. These standards and our review process, which are the same we have used in reviewing the first COVID-19 vaccine and intend to use for any other COVID-19 vaccines, included input from independent scientific and public health experts as well as a thorough analysis of the data by the agency’s career staff.”

The FDA has determined that the Moderna COVID-19 Vaccine has met the statutory criteria for issuance of an EUA. The totality of the available data provides clear evidence that the Moderna COVID-19 Vaccine may be effective in preventing COVID-19. The data also show that the known and potential benefits outweigh the known and potential risks—supporting the company’s

request for the vaccine's use in people 18 years of age and older. In making this determination, the FDA can assure the public and medical community that it has conducted a thorough evaluation of the available safety, effectiveness, and manufacturing quality information.

The Moderna COVID-19 Vaccine contains messenger RNA (mRNA), which is genetic material. The vaccine contains a small piece of the SARS-CoV-2 virus's mRNA that instructs cells in the body to make the virus's distinctive "spike" protein. After a person receives this vaccine, their body produces copies of the spike protein, which does not cause disease, but triggers the immune system to learn to react defensively, producing an immune response against SARS-CoV-2.

"Guided by science and data, the agency's career staff determined that the vaccine's known and potential benefits clearly outweigh its known and potential risks, and although not an FDA approval, the FDA's expectations described in our June and October guidance documents have been met," said Peter Marks, M.D., Ph.D., Director of the FDA's Center for Biologics Evaluation and Research. "Today's authorization demonstrates our steadfast commitment to the health of the American people, with the assurance that our scientific standards and the integrity of our review process have been maintained. This achievement is yet another testament to the dedication of FDA's career scientists and physicians, who have been working urgently to conduct comprehensive and rigorous evaluations of the data submitted for vaccines to prevent COVID-19."

FDA Evaluation of Available Safety Data

Moderna COVID-19 Vaccine is administered as a series of two doses, one month apart. The available safety data to support the EUA include an analysis of 30,351 participants enrolled in an ongoing randomized, placebo-controlled study conducted in the U.S. These participants, 15,185 of whom received the vaccine and 15,166 of whom received saline placebo, were followed for a median of more than two months after receiving the second dose. The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, swollen lymph nodes in the same arm as the injection, nausea and vomiting, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so it is important for vaccination providers and recipients to expect that there may be some side effects after either dose, but even more so after the second dose.

It is mandatory for ModernaTX, Inc. and vaccination providers to report the following to the Vaccine Adverse Event Reporting System (VAERS) for Moderna COVID-19 Vaccine: all vaccine administration errors, serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS), and cases of COVID-19 that result in hospitalization or death.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the EUA include an analysis of 28,207 participants in the ongoing randomized, placebo-controlled U.S. study who did not have evidence of SARS-CoV-2 infection prior to the first dose of vaccine. Among these participants, 14,134 received the vaccine and 14,073 received placebo. The vaccine was 94.1% effective in preventing COVID-19 disease among these clinical trial participants with 11 cases of COVID-19 in the vaccine group and 185 in the placebo group. At the time of the analysis of these 196 COVID-19 cases, none in the vaccine group and 30 in the placebo group were classified as severe. After the analysis of these 196 cases was completed, one severe case in the vaccine group was identified and is awaiting confirmation. At this time, data are not available to determine how long the vaccine will provide protection, nor is there evidence that the vaccine prevents transmission of SARS-CoV-2 from person to person.

The EUA Process

On the basis of the determination by the Secretary of the Department of Health and Human Services on Feb. 4, 2020, that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and issued declarations that circumstances exist justifying the authorization of emergency use of unapproved products, the FDA may issue an EUA to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent COVID-19 when there are no adequate, approved, and available alternatives.

The issuance of an EUA is different than an FDA approval (licensure) of a vaccine, in that a vaccine available under an EUA is not approved. In determining whether to issue an EUA for a product, the FDA evaluates the available evidence to determine whether the product may be effective and also assesses any known or potential risks and any known or potential benefits. If the product meets the effectiveness standard and the benefit-risk assessment is favorable, the product is made available during the emergency. Once a manufacturer submits an EUA request for a COVID-19 vaccine to the FDA, the agency then evaluates the request and determines whether the relevant statutory criteria are met, taking into account the totality of the scientific evidence about the vaccine that is available to the FDA.

The EUA also requires that fact sheets that provide important information, including dosing instructions, and information about the benefits and risks of the Moderna COVID-19 Vaccine, be made available to vaccination providers and vaccine recipients.

ModernaTX, Inc. has submitted a pharmacovigilance plan to the FDA to monitor the safety of Moderna COVID-19 Vaccine. The pharmacovigilance plan includes a plan to complete longer-term safety follow-up for participants enrolled in ongoing clinical trials. The pharmacovigilance

plan also includes other activities aimed at monitoring the safety profile of the Moderna COVID-19 vaccine and ensuring that any safety concerns are identified and evaluated in a timely manner.

The FDA also expects manufacturers whose COVID-19 vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and effectiveness information and pursue approval (licensure).

The EUA for the Moderna COVID-19 Vaccine was issued to ModernaTX, Inc. The authorization will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19 is terminated. The EUA for Moderna COVID-19 Vaccine may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Related Information

- [Moderna COVID-19 Vaccine EUA Letter of Authorization](https://www.fda.gov/media/144636/download)
(<https://www.fda.gov/media/144636/download>).
- [Moderna COVID-19 Vaccine EUA Fact Sheet for Healthcare Providers](https://www.fda.gov/media/144637/download)
(<https://www.fda.gov/media/144637/download>).
- [Moderna COVID-19 Vaccine EUA Fact Sheet for Recipients and Caregivers](https://www.fda.gov/media/144638/download)
(<https://www.fda.gov/media/144638/download>).
- [COVID-19 Vaccines \(/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines\)](/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines)
- [Emergency Use Authorization for Vaccines Explained \(/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained\)](/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained)
- [Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19\)](/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19)
- [Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry \(/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19\)](/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19)

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EXHIBIT 14



NEWS RELEASE

Moderna Receives Full U.S. FDA Approval for COVID-19 Vaccine Spikevax

1/31/2022

Approval based on a comprehensive submission package including efficacy and safety data approximately six months after second dose

SPIKEVAX has received approval by regulators in more than 70 countries, including Canada, Japan, the European Union, the UK, Israel

807 million doses of Moderna's COVID-19 vaccine shipped globally in 2021; approximately 25% of those doses shipped to low- and middle-income countries

CAMBRIDGE, MA / ACCESSWIRE / January 31, 2022 / Moderna, Inc. (Nasdaq:MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines, today announced the U.S. Food and Drug Administration (FDA) has approved the Biologics License Application (BLA) for SPIKEVAX (COVID-19 Vaccine, mRNA) to prevent COVID-19 in individuals 18 years of age and older.

"Our COVID-19 vaccine has been administered to hundreds of millions of people around the world, protecting people from COVID-19 infection, hospitalization and death. The totality of real-world data and the full BLA for Spikevax in the United States reaffirms the importance of vaccination against this virus. This is a momentous milestone in Moderna's history as it is our first product to achieve licensure in the U.S.," said Stéphane Bancel, Chief Executive Officer of Moderna. "The full licensure of Spikevax in the U.S. now joins that in Canada, Japan, the European Union, the UK, Israel, and other countries, where the adolescent indication is also approved. We are grateful to the U.S. FDA for their thorough review of our application. We are humbled by the role that Spikevax is

playing to help end this pandemic."

The FDA based its decision on the totality of scientific evidence shared by the Company in its submission package, which included follow-up data from the Phase 3 COVE study showing high efficacy and favorable safety approximately six months after the second dose. Moderna also submitted manufacturing and facilities data required by the FDA for licensure. SPIKEVAX has received approval by regulators in more than 70 countries.

Moderna's COVID-19 vaccine was available under Emergency Use Authorization (EUA) in the U.S. from December 18, 2020. Under an EUA, the FDA has the authority to allow medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions during a declared public health emergency when there are no adequate, approved, and available alternatives. A booster dose of the Moderna COVID-19 vaccine at the 50 µg dose level is **authorized** for emergency use in the U.S. under EUA for adults 18 years and older. A third dose of the Moderna COVID-19 vaccine at the 100 µg dose level is authorized for emergency use in immunocompromised individuals 18 years of age or older in the United States who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

INDICATION (U.S.)

SPIKEVAX (COVID-19 Vaccine, mRNA) is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older.

IMPORTANT SAFETY INFORMATION

- Do not administer to individuals with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.
- Appropriate medical treatment to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the vaccine.
- Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age.
- Syncope (fainting) may occur in association with administration of injectable vaccines. Procedures should be in place to avoid injury from fainting.
- Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished response to the vaccine.
- The vaccine may not protect all vaccine recipients.

- Adverse reactions reported in clinical trials following administration of the vaccine include pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, and erythema at the injection site, and rash.
- The vaccination provider is responsible for mandatory reporting of certain adverse events to the Vaccine Adverse Event Reporting System (VAERS) online at <https://vaers.hhs.gov/reportevent.html> or by calling 1-800-822-7967.

About Moderna

In 10 years since its inception, Moderna has transformed from a research-stage company advancing programs in the field of messenger RNA (mRNA), to an enterprise with a diverse clinical portfolio of vaccines and therapeutics across seven modalities, a broad intellectual property portfolio in areas including mRNA and lipid nanoparticle formulation, and an integrated manufacturing plant that allows for both clinical and commercial production at scale and at unprecedented speed. Moderna maintains alliances with a broad range of domestic and overseas government and commercial collaborators, which has allowed for the pursuit of both groundbreaking science and rapid scaling of manufacturing. Most recently, Moderna's capabilities have come together to allow the approval of one of the earliest and most effective vaccines against the COVID-19 pandemic.

Moderna's mRNA platform builds on continuous advances in basic and applied mRNA science, delivery technology and manufacturing, and has allowed the development of therapeutics and vaccines for infectious diseases, immuno-oncology, rare diseases, cardiovascular diseases and auto-immune diseases. Moderna has been named a top biopharmaceutical employer by Science for the past seven years. To learn more, visit www.modernatx.com.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding: the Company's development of a vaccine against COVID-19 (mRNA-1273, or Spikevax); the ability of Spikevax to protect against COVID-19 and prevent infection, hospitalization and death; and the safety profile for Spikevax. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include those other risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release in the event

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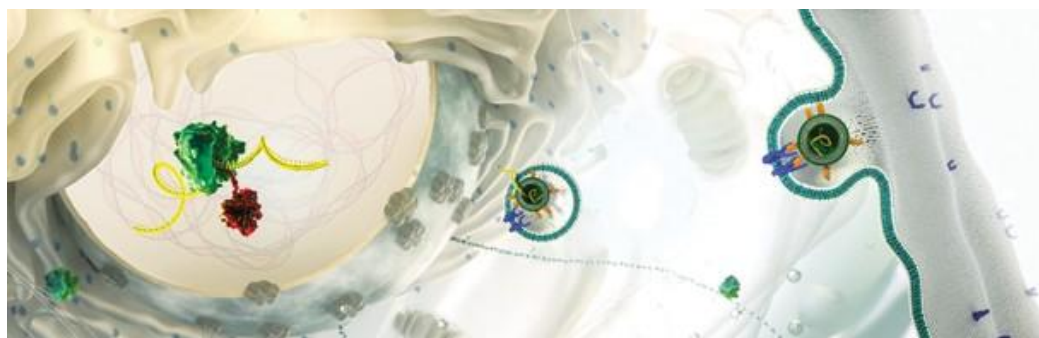
COVID-19

Without these lipid shells, there would be no mRNA vaccines for COVID-19

Fragile mRNA molecules used in COVID-19 vaccines can't get into cells on their own. They owe their success to lipid nanoparticles that took decades to refine

by **Ryan Cross**

March 6, 2021 | A version of this story appeared in **Volume 99, Issue 8**



Credit: Acuitas Therapeutics

A lipid nanoparticle (LNP) containing messenger RNA (mRNA) enters a cell through an endosome (right). When the LNP is inside the acidic endosome (middle), the ionizable lipids become positively charged and help release the LNP and mRNA into the cell's cytoplasm. Once free, the mRNA is translated by ribosomes to make proteins (left).

Messenger RNA (mRNA) is having a moment. This year, hundreds of millions of people will receive shots of the **Pfizer-BioNTech** or **Moderna vaccines for COVID-19**. The crucial ingredient in each injection is mRNA, short-lived strands of

genetic material that prompt our cells to start making SARS-CoV-2 proteins, which in turn help our immune systems develop antibodies that prevent future infections. Thanks to decades of scientific perseverance, billions of dollars of investment in the technology, and **previous work on coronaviruses**, the vaccine makers were able to design their vaccines and prove their safety and efficacy in under a year.

Related: Everything we know about the COVID-19 coronavirus

The **success of these COVID-19 vaccines** is remarkable and was far from guaranteed. mRNA is incredibly delicate. Enzymes in the environment and in our bodies are quick to chop mRNA into pieces, making lab experiments difficult and the delivery of mRNA to our cells daunting. On top of that, mRNA strands are large and negatively charged and can't simply waltz across the protective lipid membranes of cells. Many scientists **thought the technology would never work**.

"There were many, many skeptics," says Frank DeRosa, who began working with mRNA in 2008 and is now chief technology officer at Translate Bio, a firm developing mRNA vaccines with Sanofi. "People used to say that if you looked at it wrong it would fall apart."

Luckily, scientists found a solution. To protect the fragile molecule as it sneaks into cells, they turned to a delivery technology with origins older than the idea of mRNA therapy itself: tiny balls of fat called lipid nanoparticles, or LNPs.

LNPs used in the COVID-19 vaccines contain just four ingredients: ionizable lipids whose positive charges bind to the negatively charged backbone of mRNA, pegylated lipids that help stabilize the particle, and phospholipids and cholesterol molecules that contribute to the particle's structure. Thousands of these four components encapsulate mRNA, shield it from destructive enzymes, and shuttle it into cells, where the mRNA is unloaded and used to make proteins. Although the concept seems simple, perfecting it was far from straightforward.

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“It is a tremendous vindication for everyone working in controlled drug delivery.

— **Robert Langer**, chemical engineer, Massachusetts Institute of Technology

Over more than 3 decades, promising lipids studied in the lab often failed to live up to their potential when tested in animals or humans. Positively charged lipids are inherently toxic, and companies struggled for years before landing on formulations that were safe and effective. When injected intravenously, the particles invariably accumulated in the liver, and delivery to other organs is still an obstacle. Reliably manufacturing consistent LNPs was another challenge, and **producing the raw materials** needed to make the particles is a limiting factor in the production of COVID-19 vaccines today.

LNP development has been a headache, but without this packaging, mRNA vaccines would be nothing. "It is the unsung hero of the whole thing," says Giuseppe Ciaramella, who was head of infectious diseases at Moderna from 2014 to 2018.

The vaccines, appropriately celebrated as a first for mRNA technology, are also a milestone for the nanoparticle field. Although **the first drug based on an LNP** was approved by the US Food and Drug Administration for a rare genetic disease in 2018, the two authorized mRNA vaccines for COVID-19 present a far bigger opportunity for the nanoparticles than even the field's founders can imagine. "It is a tremendous vindication for everyone working in controlled drug delivery," says Robert Langer, a chemical engineer at the Massachusetts Institute of Technology.

"LNPs will be going into millions of arms over the course of this year," says University of British Columbia nanoparticle scientist Pieter Cullis. "What was a fringe field back in the 1980s has turned into something that is mainstream now."

THE DELIVERY DILEMMA

Modern LNPs can be traced back to work on simpler systems called liposomes, hollow lipid spheres often made of just two or three kinds of lipids. In the early 1980s, Cullis found that cancer drugs could diffuse into these liposomes and get trapped in the hollow core. When injected into animals with cancer, the liposomes would slip through the leaky vasculature of tumors, enter cells, and unleash a drug. Cullis, and several others, started companies with the hope that liposomes could safely deliver otherwise toxic drugs into tumors in humans.

Progress was slowed by issues with stability and manufacturing. The first liposome-based drug eventually was approved by the FDA in 1995, but by then Cullis and many in the field had moved on to a new challenge: using lipid particles to deliver nucleic acids such as DNA and RNA.

“The devil is absolutely in the details as far as LNPs are concerned.

— **Giuseppe Ciaramella**, former head of infectious diseases, Moderna

At the time, scientists were enamored by advances in genetics that were promising to cure diseases by giving someone new genes or turning disease-causing genes off. Figuring out how to deliver these nucleic acid therapies—either DNA or RNA—into cells was a major challenge and required something more sophisticated than a conventional liposome. Cullis knew that adding positively charged lipids to the liposomes would help balance the negatively charged nucleic acids, but there was a problem. “There are no cationic lipids in nature,” Cullis says. “And we knew we couldn’t use permanently positively charged lipids because they are so damn toxic.” Those lipids would rip cell membranes apart, he adds.

A solution came from new lipids that were charged only under certain conditions. During the late '90s and through the first decade of the 2000s, Cullis, his colleagues at Inex Pharmaceuticals, and the Inex spin-off Protiva Biotherapeutics developed ionizable lipids that are positively charged at an acidic pH but neutral in the blood. The group also created a new way to manufacture nanoparticles with these lipids, using microfluidics to mix lipids dissolved in ethanol with nucleic acids dissolved in an acidic buffer. When the streams of those two solutions merged, the components spontaneously formed lipid nanoparticles, which, unlike the hollow liposomes, were densely packed with lipids and nucleic acids. The process was simple in theory, but getting the machine to reliably spit out consistent LNPs was difficult.

LNPs that looked good in the lab often floundered in the clinic, however. The first versions of ionizable lipids were still toxic. And early formulations of the nanoparticles didn’t degrade fast enough, causing them to accumulate after repeated injections. Protiva found that one of its experimental LNP therapies caused a more severe immune reaction in humans than it had in the lab, and the company pinned pegylated lipids as a major factor.

Related: This was mRNA’s breakout year, and scientists are just getting started

Pegylated lipids, in which polyethylene glycol (PEG) strands are attached to lipid heads, have several functions in a nanoparticle. PEG helps control the particle size during formulation, prevents the particles from aggregating in storage, and initially shields the particles from being detected by immune system proteins in the body, according to James Heyes, a former Protiva scientist. Heyes is now chief scientific officer of the LNP company Genevant Sciences—a firm with origins in Protiva.

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But PEG also has liabilities. It prevents LNPs from binding to proteins that help shuttle them into cells. Because PEG extends particles' life span in the body, the immune system has more time to spot the particles and start mounting an antibody response. And although PEG is found in many cosmetic, drug, and food products, scientists hypothesize that some people could develop antibodies to PEG and that giving those individuals an injection of PEG-coated nanoparticles could trigger an anaphylactic reaction.

ESCAPE FROM THE ENDOSOME

By 2005, the development of better and safer LNPs was **driven by excitement for a new technology, called small interfering RNA (siRNA), for selectively silencing genes.** Alnylam Pharmaceuticals, which became the leading siRNA company, quickly realized that existing nanoparticles were not very good at helping siRNA get into cells. The company struck multiple partnerships to make new LNPs, including with Protiva in 2005 and Inex in 2006. The groups made more than 300 ionizable lipids, first optimizing the fatty tails, then tweaking the ionizable head group and the linker region in between. The work was grueling, and lipids that made great nanoparticles in a petri dish would often flop in animal studies. "You can have 50 different ionizable lipids that all deliver effectively to cells in culture, and 49 of them won't work a damn in vivo," recalls Thomas Madden, who worked at Inex and is now CEO of Acuitas Therapeutics.

LNPs take advantage of a natural process called receptor-mediated endocytosis to get into cells, Madden explains. Upon binding to a cell, the nanoparticle becomes encapsulated in an even bigger lipid bubble—an organelle called an endosome. The endosome's acidic interior protonates the heads of the ionizable lipids, making them positively charged. That positive charge triggers a change in the shape of the nanoparticle, which scientists think helps it break free from the endosome and ultimately release its RNA cargo into the cell's cytoplasm. Once released, the RNA is free to do its job.



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The most effective nanoparticles were ones that the body mistook as low-density lipoprotein (LDL) cholesterol—commonly called bad cholesterol. Proteins that recognize LDL cholesterol in the blood bound to some of Alnylam's nanoparticles and carried them to LDL receptors on liver cells, which then caused the cells to engulf the nanoparticles in an endosome. It was the kind of complex interplay that studies in a petri dish missed.

"A lot of work has gone into studying what happens inside a cell, but trying to understand the transport that occurs before these nanoparticles reach their cells is another question entirely," says Kathryn Whitehead, a

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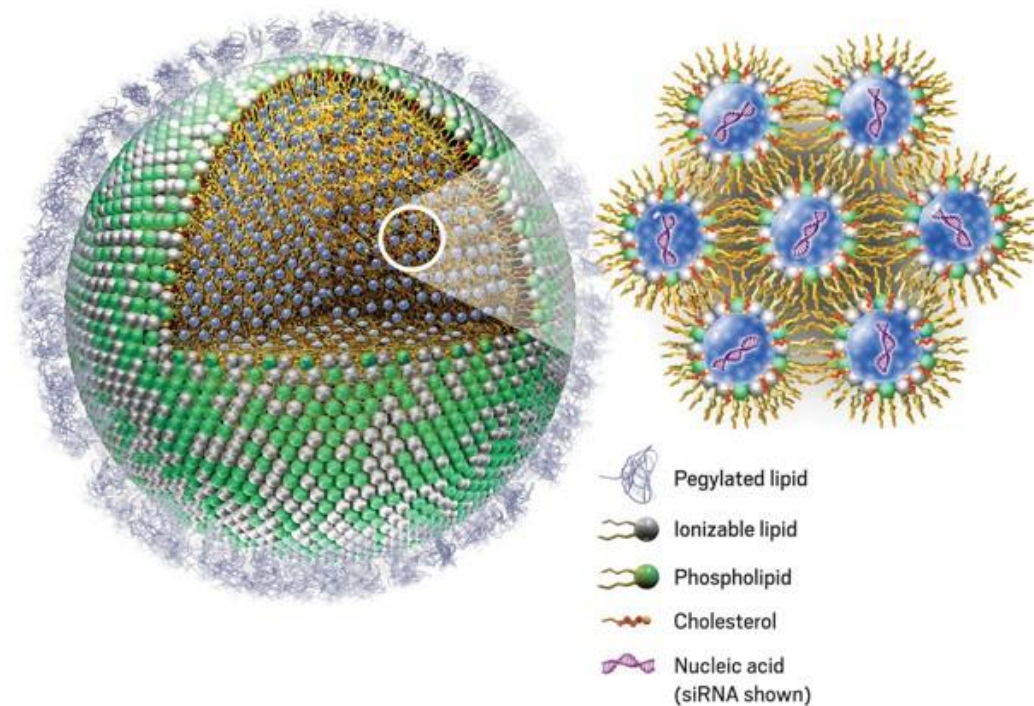
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PARTS LIST



A lipid nanoparticle (LNP) contains hundreds of small interfering RNA (siRNA) molecules, each surrounded by ionizable lipids, phospholipids, and cholesterol. The outside of the particle is coated in pegylated lipids. LNPs for messenger RNA (mRNA) are made with similar ingredients but contain only a few mRNA strands.

nanoparticle scientist at Carnegie Mellon University. As a consequence, “we don’t even screen in vitro anymore,” she says. “I find it more informative to test directly in an animal.”

Even some of the LNPs that worked well in animals proved too toxic for the repeated dosing required of many siRNA therapies. “The biggest issue was trying to find the right balance between systems that were effective but also safe and tolerable,” says Marian Gindy, executive director of pharmaceutical sciences at Merck & Co., who led the RNA formulation team from 2008 until Merck ended its siRNA programs in 2013. “And I would say that is still the biggest challenge in this area.”

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By 2010, Alnylam had landed on a winning ionizable lipid known as MC3. Nanoparticles based on MC3 required about one-thousandth the dose of LNPs made using older ionizable lipids. Alnylam used the new formulation in patisiran (Onpattro), its treatment for a rare disease called hereditary transthyretin-mediated amyloidosis. In 2018, patisiran became **the first approved siRNA drug** and the first approved therapy delivered via LNPs. But the drug requires an 80 min infusion every 3 weeks and pretreatment with multiple anti-inflammatory drugs to minimize reactions to the nanoparticle. By the time patisiran was showing promise in the clinic, Alnylam had set most of its LNP work aside in favor of a new chemical

conjugation technology that it used to deliver its other siRNA therapies subcutaneously.

A LAUNCHPAD FOR MRNA

For a brief time, new work on LNPs fell out of favor—that is, until new companies that were focused on mRNA brought fresh energy to the field. BioNTech, founded in 2008, and Moderna, founded in 2010, promised to be able to use mRNA to produce any protein in the body, as either a therapeutic or a vaccine. In the past decade, mRNA garnered **billions of dollars of investment**. Discovering how to deliver those mRNA strands into cells was a problem from day 1, but prior experience with siRNA provided a launching pad.

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“Early on people recognized that the same lipids used for siRNA could also be useful for mRNA,” says Daniel Anderson, a nanomedicine and biomaterials scientist at MIT. His group began collaborating with the rare-disease company Shire Pharmaceuticals to encapsulate mRNA that encoded protein therapies to treat rare liver diseases.

Related: Delivering The Promise

The off-the-shelf LNP formulations designed for siRNA worked for mRNA occasionally but not very well, says Romesh Subramanian, who led a team at Alexion Pharmaceuticals that worked on mRNA therapies with Moderna from 2014 to 2017. siRNA molecules are like short rods, with two rows of about 20 nucleotides each, he explains. mRNA, in contrast, can easily span thousands of nucleotides, wind into complex shapes, and change the properties of the LNP in ways that are hard to predict.

After realizing that MC3 wouldn't cut it for mRNA delivery, Moderna invested significant resources into building a better ionizable lipid. “There was a group of chemists put on this right away to build novel cationic lipids,” says Ciaramella, the former head of infectious diseases at Moderna. “It is kind of like a small-molecule drug discovery engine, but on steroids.” The team made about 100 ionizable lipids and introduced ester linkages into the carbon chains of the lipids to help make them more biodegradable, he recalls. Tweaking the ratio of the four lipids in the nanoparticles altered the LNPs' distribution in the body. “The devil is absolutely in the details as far as LNPs are concerned,” Ciaramella says. “But once you optimize it for one organ, you can change out the mRNA with minimal optimization.”

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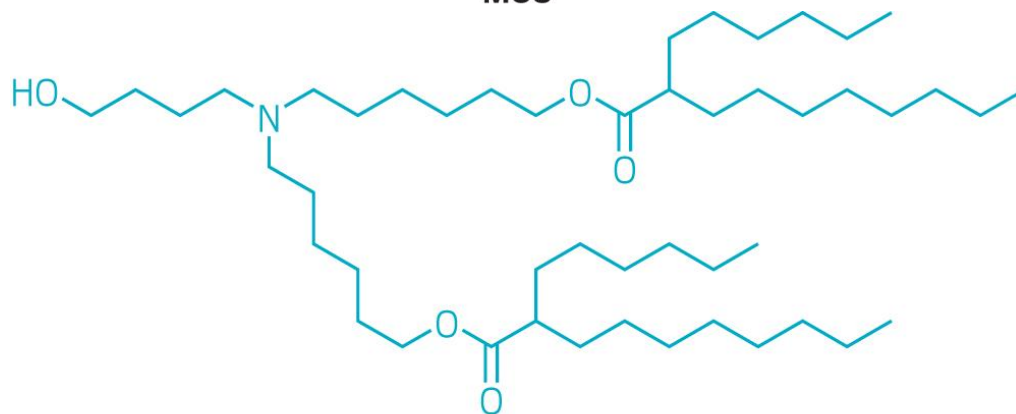
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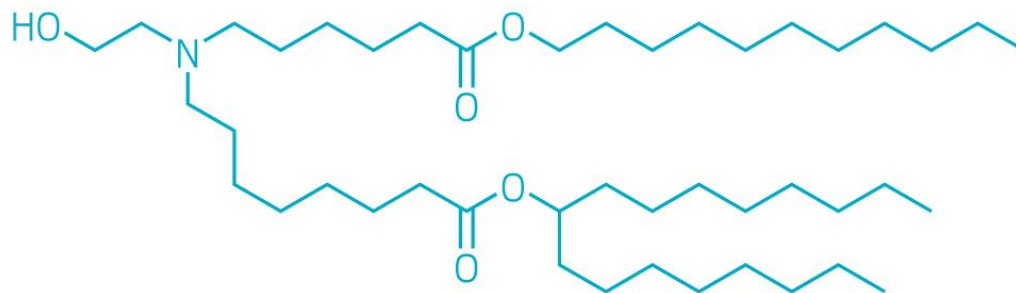
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MC3



ALC-0315



SM-102

That adaptability is key. For example, Moderna recently made an updated version of its COVID-19 vaccine for a **new variant of the coronavirus** first identified in South Africa. In that vaccine, which must still undergo clinical testing, the mRNA code is slightly changed to match the genetic code of the new strain of the virus, but the LNP formulation remains the same. Now that the company knows its nanoparticle works, it can use it over and over again for different vaccines.

But details on how Moderna arrived at its optimal formulation in the first place are scant. The company did not grant an interview to talk about its nanoparticle development, and neither did Pfizer or BioNTech. For its COVID-19 vaccine, Moderna ultimately used an ionizable lipid that it calls SM-102, which it first described in a 2018 study on alternatives to MC3. Pfizer and BioNTech licensed an ionizable lipid called ALC-0315 from Acuitas.

Those ionizable lipids, which are remarkably similar in structure, were discovered while the firms were optimizing LNPs for systemic administration and delivery to the liver—not the intramuscular injection of a vaccine. Experts point out that optimizing the nanoparticles for vaccination could lead to shots that require lower doses, which could ease the manufacturing burden amid a pandemic. New lipids and nanoparticle formulations will likely take too long to develop to make a difference during this pandemic, but Moderna, BioNTech, and others are continuing to look for better ways to get mRNA into cells for a variety of applications.

AN LNP RESURGENCE

The pandemic has reinvigorated interest in continuing to refine LNPs. Small firms dedicated to the nanoparticles are getting more calls from larger drug companies that want to use their lipids. Effective LNPs could be crucial for new mRNA vaccines, mRNA therapies, DNA gene therapies, and even CRISPR gene-editing therapies.



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“Everyone is trying to figure out the next big ionizable lipid,” says Gaurav Sahay, a nanoparticle scientist at Oregon State University. But he thinks that nanoparticle researchers should also start paying more attention to the other components of an LNP. Sahay says his lab found that using alternative versions of cholesterol molecules could dramatically improve delivery. And although both the Moderna and Pfizer-BioNTech vaccines use the same standard phospholipid, swapping out this ingredient for a different phospholipid could lead to nanoparticles that reach different cells in the body, Whitehead says.

“Delivery into specific cell and tissue populations is still a huge challenge for the field,” says Yizhou Dong, a nanoparticle researcher at the Ohio State University. Right now, intravenous injections of nanoparticles can easily reach the liver, and intramuscular injections for vaccines are taken up by immune cells. Some companies are working on experimental formulations for aerosolized delivery to the lungs, but the rest of the body remains out of reach, and the demand for targeted delivery is high. In late February, the **CRISPR base-editing** company **Beam Therapeutics**, where Ciaramella is president and chief scientific officer, **paid \$120 million** to acquire the start-up Guide Therapeutics, which is focused on LNP discovery and has a system for finding particles that target specific cells of the body.

Related: Delivering RNA Interference

“There was this time when LNPs went through the dark ages,” says Thomas Barnes, CEO of the mRNA company **Orna Therapeutics**. “I think there is going to be a bit of a renaissance in these ionizable lipids and that the world is going to get excited about LNPs again.”

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For now, the success of the COVID-19 vaccines is a sweet victory. “It is a little surreal, honestly,” Anderson says. “It is something that we went from just being excited about to something that my mom got in a shot in January.”

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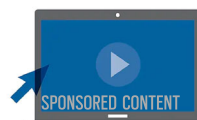
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EXHIBIT 16

**Hearing Before the House Energy and Commerce Committee
Subcommittee on Oversight & Investigations**

**Testimony of Dr. Stephen Hoge
President, Moderna, Inc.**

July 21, 2020

Chairwoman DeGette, Ranking Member Guthrie, and distinguished Members of the Subcommittee, thank you for the opportunity to appear before you today. My name is Stephen Hoge, and I serve as the President of Moderna, Inc. (“Moderna”). I am proud to work for a company that is developing one of the vaccine candidates, mRNA-1273, for the treatment of SARS-CoV-2, the novel strain of coronavirus causing the devastating global COVID-19 pandemic.

We recognize the extraordinary harm the pandemic has done to millions of Americans. Our hearts go out to those who have lost loved ones or have been sick themselves. Millions of Americans are out of work. Others, like my wife and I, work to balance parenting with our professional obligations. My wife is a practicing physician, as are several members of my family, and I have seen how profoundly healthcare providers have been challenged by COVID-19. The pandemic has postponed weddings, cancelled graduations, and kept people away from funerals. All of us have been profoundly touched by this in some way. We also know that communities of color and the working class have disproportionately borne the burdens of COVID-19. We must do everything we can to stop this pandemic.

I understand there is significant interest in the work of Moderna and the companies who have witnesses testifying today. People all over the world want to know when we might be able to return to some sense of normalcy. People want to know how they can best protect their relatives and others. People want to go back to work. Others miss the ability to easily see their friends or family. Parents want their kids to continue their education, and their children want to play with their classmates. People also want to know that the taxpayer funds invested in potential vaccine candidates will pay off. I hope that my testimony today will provide further information about how Moderna—like the other companies testifying today and others not present here—is working as hard as it can to fight the COVID-19 pandemic. This may provide comfort to people in America and around the globe.

I feel fortunate to be in a company that is now working toward a scientific response to this current crisis. I joined Moderna eight years ago to do something like this and meet significant scientific challenges. My background is in medicine. I attended medical school at University of California San Francisco and briefly served as a resident in the emergency medical department at a New York City hospital. A decade later, while consulting for companies in the healthcare sector, I learned about a ten-person start-up pursuing a revolutionary approach to

treating disease: Moderna. If it worked, the vision and technology driving the company could unlock new frontiers for medicine. The chance to pursue that future is why I joined Moderna.

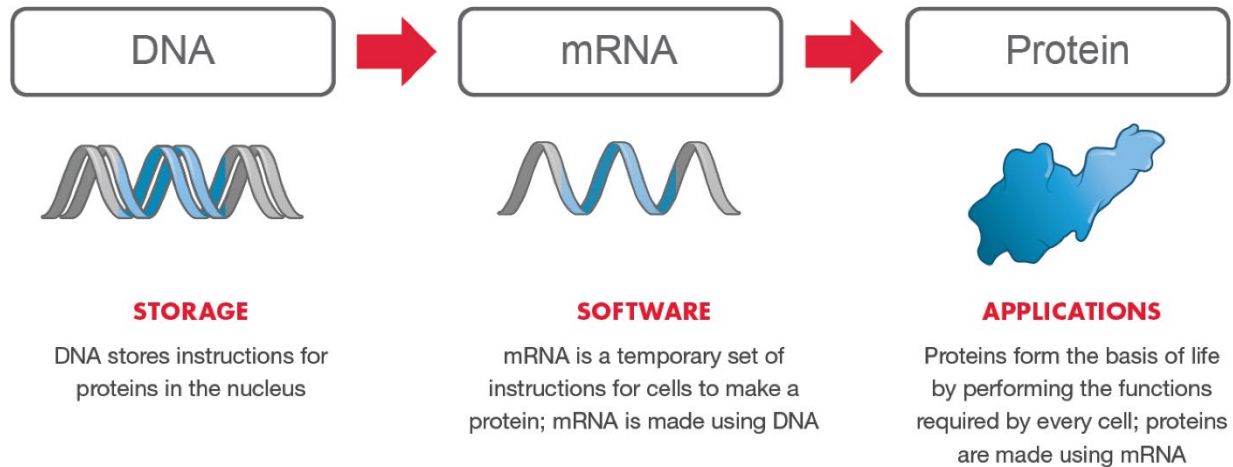
Over the past few months, Moderna has been pleased to collaborate with the U.S. government during the development of our vaccine candidate. This collaboration includes not only working together to test a possible COVID-19 vaccine, but also to build the manufacturing and distribution capacity needed to deliver a safe and effective vaccine to the American people. As we move into Phase 3 of our mRNA-1273 clinical trials, we remain committed to maintaining an ongoing dialogue with key U.S. government agencies to ensure that our work proceeds as quickly and safely as possible.

I'd like to take this opportunity to describe Moderna and our efforts to develop a vaccine that will be effective against COVID-19. *First*, I'll give you a brief overview of our mRNA technology and how it works. *Second*, I'll explain the process we used to develop our COVID-19 vaccine. *Finally*, I'll provide an update on the current status of our efforts. I appreciate deeply the opportunity to appear before you today, and we at Moderna are profoundly grateful for the actions you and your colleagues in Congress have taken to support and fund efforts to combat this pandemic.

I. Moderna is an Innovative Company That Has Built Unique mRNA Technology

Moderna is a young, innovative biotechnology company that seeks to improve patients' lives by creating a new generation of transformative medicines based on messenger RNA ("mRNA"). Founded in 2010, we are proud to be an American company, with our headquarters and a major manufacturing facility in Massachusetts. Moderna has grown over the past decade into a dynamic company with over 800 employees—a far cry from the ten-person startup that I first encountered. This exceptional team—which has worked in collaboration with leading biopharmaceutical companies, U.S. government agencies, and private organizations focused on public health—has disclosed twenty-four therapeutic and vaccine development programs to date. These programs span a wide range of diseases and conditions, including infectious diseases, immuno-oncology, rare diseases, autoimmune diseases, and cardiovascular diseases.

At Moderna, we create medicines by using messenger RNA, or mRNA, which plays a fundamental role in human biology. All human genetic information is stored in DNA located in a cell's nucleus. In order to access that information, cells need to make a working copy of it—that is mRNA. Unlike DNA, mRNA molecules move out of a cell's nucleus; once outside the nucleus, mRNA molecules transfer the information they encode to the cellular machinery that make all the proteins required for life. Each mRNA molecule contains the instructions to produce a specific protein with a distinct function in the body. mRNA thus plays a central role in all biological processes, including in human health and disease, which is why we call it the "software of life."



Our approach fundamentally differs from traditional approaches to medicine. Rather than introduce a protein or chemical to the body, we send tailored mRNA into cells to instruct them to produce specific proteins. We built Moderna on the guiding premise that if mRNA can be used as a medicine for one disease, it could work for many diseases. Instead of starting from scratch for each new vaccine or therapy, our mRNA approach leverages the technology and fundamental components that we have been researching and developing since our founding. By building off our prior research and learning, we believe we can improve how we discover, develop, and manufacture medicines.

We designed our strategy and operations to realize the full potential value and impact of mRNA over a long time-horizon. Since 2010, we have built and invested in our technology platform, which creates mRNA sequences that cells recognize as if they were produced in the body. Our prior research and clinical trials taught us valuable lessons about designing vaccines—particularly how to manufacture mRNA that can be safely injected into people and induce an appropriate immune response. We believe this platform can be used to pursue mRNA medicines for a broad spectrum of diseases.

Creating a new generation of medicines is a challenging endeavor. Over the past ten years, Moderna raised over \$5 billion in funding from our strategic collaborators and investors who recognize the potential of our unique mRNA approach. We are also grateful for approximately \$58 million in grant funding from the Defense Advanced Research Projects Agency (“DARPA”) and the Biomedical Advanced Research and Development Authority (“BARDA”). And in April, BARDA committed to fund up to \$483 million to accelerate the clinical development and manufacturing scale-up of our coronavirus vaccine candidate.

II. Moderna Has Used its mRNA Platform to Develop a Promising COVID-19 Vaccine

As the spread of COVID-19 across the globe has shown, the virus will not wait for the development of a vaccine. Lives depend on finding multiple safe, effective vaccines as soon as

possible. Because our mRNA technology is flexible and quickly adaptable, we stepped forward and pursued the rapid development of a COVID-19 vaccine candidate named mRNA-1273, focused always on making it as safe and tolerable a candidate as possible. We collaborated with the Vaccine Research Center and Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases (“NIAID”), which is part of the National Institutes of Health (“NIH”), in January to try to accelerate our vaccine candidate.

The story of mRNA-1273 really begins before any of us had ever heard of COVID-19. Since 2015, Moderna has worked to develop mRNA vaccines for coronaviruses, such as the SARS and MERS viruses. That experience, and Moderna’s own proprietary technologies developed through years of research, put Moderna in a unique position to respond to the current pandemic.

For example, a key challenge in developing mRNA vaccines and treatments has been to develop a vehicle for getting the mRNA into the cell—in other words, the “packaging” for shipping the mRNA software into the cell. You need technology that both protects the mRNA in transmittal and will not be mistakenly targeted by the body’s natural defenses. After years of effort, Moderna has developed a proprietary lipid-nanoparticle-delivery system that enhances safety and tolerability. We have also invested significantly in the manufacturing process to invent the technological capabilities necessary to manufacture our potential mRNA medicines.

We have been able to research and develop mRNA-1273 so quickly because we leveraged our prior research on vaccines and other mRNA-based medicines. In addition to the technology described above, this prior knowledge includes our understanding of the safety of our platform and our experience producing over 100 batches of mRNA for use in human clinical trials in just the last two years.

In our prior work on betacoronavirus mRNA vaccines, we identified a key protein on the surface of coronaviruses, called the Spike protein, as a good vaccine candidate. The identified Spike protein has two primary functions: it (i) facilitates the attachment of the coronavirus to the host cell in an individual; and (ii) contributes to the entry of the coronavirus into the host cell by fusing viral and host membranes. We began to develop mRNA-1273 by reviewing the genetic sequence of the SARS-CoV-2 Spike protein. Based on the sequence for the Spike protein, we designed and synthesized a corresponding mRNA sequence—in other words, the genetic software that will instruct a human cell to create the Spike protein. Using our validated mRNA vaccine platform, we have been able to formulate this mRNA by incorporating lipid nanoparticle technology into a vaccine that can be administered directly to a patient. Once injected, the mRNA molecule causes the patient’s cells to produce the Spike protein, which the body’s immune system then attacks, triggering a protective immunological response.

Our approach to a COVID-19 vaccine differs from traditional vaccine development because we are not injecting into the body a dead or weakened version of the coronavirus or one of its components. Instead, we used the information from the virus to teach the cells in a patient’s body how to make the virus’s spike protein, which then provokes a protective immune

response. Using this novel approach, we progressed from genetic sequencing to a vaccine ready for human testing in just 63 days, a testament to the 10 years of investment and hard work on our platform. Now, just over six months from the sequencing of the virus, Moderna is about to become one of the first U.S. companies to enter a Phase 3 trial for a vaccine candidate, with 30,000 participants. While we pursue this mission with speed, we have been, and remain committed to, prioritizing safety and effectiveness. I am grateful for the hundreds of scientists and other Moderna employees whose hard work and sacrifice have made our rapid progress possible.

III. Moderna's Progress Toward a Vaccine

I would like to give you an update on the current status of our work. Right now, we are focused on two important tasks: *First*, testing mRNA-1273 in clinical trials to assess its safety and efficacy. *Second*, developing and scaling our manufacturing and distribution capacity for mRNA-1273. I will first describe the status of our clinical trials.

As I noted above, we began work on mRNA-1273 immediately after the genetic sequence of the novel coronavirus was released on January 11, 2020. Only 25 days later, on February 7, 2020, Moderna completed its first clinical batch of mRNA-1273. The Phase 1 study, led by NIH, dosed its first participant on March 16, 2020. On May 18, 2020, we announced positive interim results from the mRNA-1273 Phase 1 study, which showed the generation of neutralizing antibody titer levels in all eight initial participants. A fuller set of interim data and results of the Phase I study were recently published by the NIH with other authors in the *New England Journal of Medicine*, which are consistent with and expanded on the interim results disclosed by Moderna on May 18, 2020. The vaccine showed neutralizing antibody titers in all forty-five participants evaluated.

The first participants in our Phase 2 study were dosed on May 29, 2020. We completed enrollment of all 600 subjects in our Phase 2 study on July 8, 2020. The Phase 2 study is ongoing.

We are set to begin our Phase 3 trial this month. 30,000 participants are expected to enroll in a randomized and placebo-controlled study, conducted in collaboration with NIAID. Each participant receiving mRNA-1273 will be dosed at 100 µg, the level Moderna has selected as the optimal dose to maximize the immune response while minimizing adverse reactions. Like the earlier Phase 1 and Phase 2 trials, the Phase 3 is a two-vaccine regimen with the doses delivered 28 days apart. The primary focus of our Phase 3 trial is determining whether mRNA-1273 can prevent symptomatic COVID-19 diseases, along with other secondary considerations, such as whether the vaccine can prevent severe COVID-19 disease.

We, along with the rest of the world, will eagerly await the results from these trials. If our vaccine is proven to be safe and effective, the Food and Drug Administration ("FDA") will be responsible for determining whether, when and under what conditions mRNA-1273 is approved.

We have also been working to develop and scale our manufacturing and distribution chains for mRNA-1273. These efforts have been partially facilitated by a \$483 million grant awarded from BARDA, as well as \$1.3 billion of recent investment from our shareholders. These have helped to lay the foundation for, if mRNA-1273 is proven safe and effective, the efficient manufacture of the vaccine and transfer into the appropriate distribution channels for the vaccination of Americans. Recognizing the need to have a robust manufacturing capability that can be executed at scale quickly, we announced a long term agreement with Lonza Ltd., a Swiss-based company with manufacturing sites in the U.S. and elsewhere, which should allow us to reach an annual manufacturing capacity of more than 500 million doses for worldwide usage.

* * * * *

As the COVID-19 pandemic spread across the world, Moderna hoped and believed our groundbreaking technology could make a positive difference. With the support of our dedicated team of employees, our Board of Directors, our shareholders, and our collaborators in the U.S. government, we stepped forward to pursue the safe and rapid development and manufacture of our vaccine candidate, mRNA-1273.

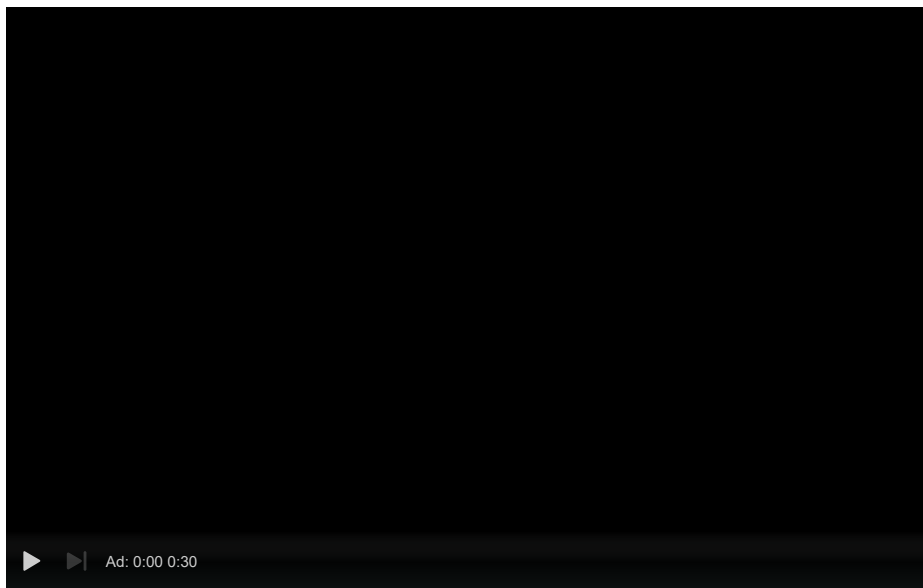
This is an unprecedented challenge, and no one has ever done anything like this before—not Moderna, not the NIH, and not any of the other companies working to stop this pandemic. While these are trying times, we are dedicated to creating a safe, effective vaccine that can help bring an end to the global pandemic. We remain committed to collaborating with the U.S. government in this process.

Thank you, and I look forward to your questions.

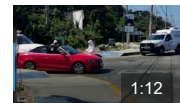
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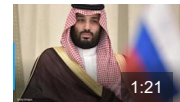
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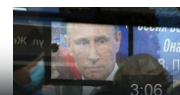
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Yahoo Finance Presents: Moderna CEO Stéphane Bancel

February 24, 2021

In this episode of Yahoo Finance Presents Moderna CEO Stéphane Bancel, talks to Yahoo Finance senior reporter Anjalee Khemlani about the company's new boosters for COVID-19 variant strands as well as the continued rollout of their vaccines.

TRENDING

1. US, China officials meet on Chinese support for Russia
2. Russians try to sell Big Macs for around \$36 each and a McDonald's paper bag for more than \$300, following the closure of branches

Video Transcript

[MUSIC PLAYING]

ANJALEE KHEMLANI: Joining me now is Stephane Bancel, CEO of Moderna. Stephane, thank you so much for joining me today.

STEPHANE BANCEL: Thank you so much for having us.

ANJALEE KHEMLANI: So great news, you have the booster shots that target specifically the B 1351 South Africa variant being submitted for clinical studies by the NIH. Let's talk a little bit about that. Clearly has been a pretty short amount of time going to the point that the company has said that tweaks are going to be pretty quick. This is just the first example of that. What are you expecting in terms of results?

STEPHANE BANCEL: So we are expecting that we should have very high efficacy and high neutralizing antibody. If you think about it, the power of mRNA is its genomics medicine. And so we literally copied the new sequence of South Africa virus and dropped it into the same cassette, everything the same that we used for the authorized vaccine that we developed last year.

So I would expect the same very neutralizing antibody and the efficacy, which is why I think mRNA between the high efficacy, we are seeing compared to other technologies and the speed to deployment which we saw last year, which we are seeing again today on the variants, is going to be very powerful to chase this virus.

And the other piece, too, is the ability to combine mRNAs. We have already put in the clinic a vaccine against CMV, cytomegalovirus, which is moving to phase three. And that has six mRNA molecule in one dose. And so if the world, if a virus and the evolution process, if human mutation in the next few months are of concern, we will chase all of those. We can combine them as biology, ask us to do to keep a high efficacy vaccine, so we can protect via boosting Americans and people in the world.

ANJALEE KHEMLANI: And I know, of course, the production of that is going to be sort of the next hurdle. You had, looking at starting basically from scratch when you started to produce the original vaccine, in large part because the technology that

3. Russia Facing 'Outright Defeat' And 'Sudden' Collapse In Ukraine, Author Says
4. Zelenskyy says Ukraine still in daily talks with Russia; US journalist killed by Russian gunfire: March 13 recap
5. British businessman victim of execution-style hit in Mexican tourist zone

you're using is so new. Whether it's raw material, like liquid nanoparticles, or just general vaccine production equipment.

The access to all that and the buildup of all that has been, of course, a very storied experience. Though you have partners like Lonza and Catalent to help with the process, you're looking at expanding right now. And we won't see that for the next year or so. So explain what that process is like and why it's such good news right now.

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STEPHANE BANCEL: Yes, so basically, as you know, we have had a lot of orders from many governments around the world. And what is very clear in the last 30 to 60 days, there's a lot of concern out there by governments who want to make sure they stay ahead of a pandemic. As you know, the death toll, the economic impact, as we all know, has been horrific in the last 12 months. And this winter, you know, has been very, very hard, and still is very, very hard. We're still losing a lot of people every day.

And the world leaders are very worried that if there's a variant of concern, especially as you might see waning immunity over time, especially of the elderly, as we know, as we get old, humans, our immune system becomes weaker. So what is unknowable today is what will be the efficacy of any vaccine six months, 12 months from now if you are infected by a new strain that seems problematic, like the one first identified in South Africa.

And so what we want to do based on that feedback from the government, that they want more. Some already, like the European Union, has put an option for 150 million doses for 2022 already. That was announced last week. And so when we look at the demand coming from the countries, we thought, geez, we believe that's 1.2 billion doses for next year was going to be plenty.

And we think we most probably were wrong last year, that it's not enough. Because, so what we didn't know last year, is that the different vaccine were going to have different efficacy. Our vaccine, as you know, has very high efficacy. So we are seeing much more demand than we could have anticipated, even in an optimistic scenario last year.

And so what we decided to do and we are announcing today is moving the capacity for 2022 to 1.4 billion doses. If you

assume 100 microgram, the dose of a current authorized vaccine. But what we announced in our variant boost strategy, is we believe that we should have good efficacy of a boost at 50 microgram all over.

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Why? Because if you've already got vaccinated, your immune system has been already educated. And so you are boosting it to get back those antibodies to a good level, to educate your immune system on the new antibodies you need on the new variants. And so we believe that those could be lower. We have, of course, to prove it in the clinic in the next few months.

But if that was the case that the boosts at 50 microgram, then the mix will play of how much output can you get out of a system. 1.4 billion at 100 microgram. If you push it to only being a boost company, that means, only boost just [INAUDIBLE], that gets you to close to 2.8 billion doses. And of course, if you can have only 50-50 scenario in term of doses output at the two dose level, that's another 2 billion capacity output for '22. So we think that it really positioning Moderna to grow from a very strong 2021 revenue projection to an even stronger next year.

ANJALEE KHEMLANI: Let's talk about that. The buildup, let's go back to the beginning when you had to start building up for the original strain and for the original doses last year. What was it that you initially experienced as hurdles that with the help of the federal government and through your partners you were able to overcome?

STEPHANE BANCEL: So the first challenge we had was just enough equipment for just capacity. Because to give you a reference, in 2019 we made less than 100,000 dose over year. Because as you mentioned, we are not a commercial company. We're a clinical development company. And so if you look at the number of what we shipped to the US government, which is now around 17 million doses in December, it means that we made those doses through 2020, exactly a 200x increase just in 12 months, which is remarkable.

And so we bought machines, we scaled up a process, mean bigger and bigger reactor, so we can more and more product per unit of time. We did that in a factory in Massachusetts. We did that in Lonza in New Hampshire, we did it in Lonza in

Switzerland. And then we have to deal with filling. Because a filling capability, we have a plant is only for clinical trials.

Thousands of those at the time, not hundreds of millions. And so we partnered with Catalent, who's doing a remarkable job.

We partnered with Rovi in Spain. We partnered with Recipharm in France. And we will add filling capacity as we keep building the drug substance of a vaccine capacity.

ANJALEE KHEMLANI: And what about the substance? I know there's been a lot about the fact that the lipids, you know it hasn't been as widespread use-wise to the point of just in clinical. But to be able to scale that up, is that something you're looking to bring in house or have the capacity to?

STEPHANE BANCEL: So it's a different technology than mRNA, because it's a small molecule, more like traditional pharmaceutical product. So this early PEI that we invented in our labs that is biodegradable, so it's a big competitive advantage for us. But we have been working with our partners right away. I think the challenge we had, our head of manufacturing, he used to be the head of manufacturing of Novartis worldwide. He had been with us three years before the pandemic hit, so known us and the process very well and so on.

And so what we did last year when I challenged Juan back in February to say, hey, how do we go to a billion does, I think what has happened Moderna a lot, as a new commercial company is, we aim for a big number of very early on in the race against the virus. And we say, OK, how do we get to a billion? And so that allowed us by thinking big from the get-go, to think really outside the box, but also to give guidance to our suppliers.

And so one way we also helped our lipid suppliers is, we purchased by paying upfront cash a lot of product. Because they, in their turn, had to go buy machines and hire people. And they were worried, because they say, look, if the product fails in the clinic, you might go bankrupt and not pay us. So these were the type of issues we had to deal with last year.

And the way we dealt with it is, we funded upfront the raw material of supply. And if you remember, we did a big capital raise. On May 18, we raise \$1.3 billion. And if you look at the SEC document, the proceeds of that raise were to buy

machine, buy materials, and hire people to make the COVID-19 vaccine that was at the time, a candidate. And so I think us being aggressive and us being able to afford to put our balance sheet at risk to help our suppliers in their turn, raise capacity, was very important I think.

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ANJALEE KHEMLANI: And looking at the production,

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increasing that target for next year, not that but you have all of this in swing, what specifically is part of that expansion? What parts of it are the expansion that you're looking at that's going to help you get to that \$1.4 billion?

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STEPHANE BANCEL: So a bit of everything in the process, meaning we need making more mRNA mass. We need to do more formulation of lipid. And of course, more filling. So it's really the entire. When you add a big stream of capacity, like by 100 million at the time, basically you need to increase capacity everywhere, because you have bottlenecks everywhere.

ANJALEE KHEMLANI: So now looking forward, the company have had a validation, like others in the space really. It seems like this pandemic has been, as we've discussed, almost a bright spot for you being able to validate not just the technology, but also the company and look for your pipeline going forward. Have there been discussions, are you working simultaneously on this? Or does the COVID vaccine still take up a lot of the time and energy and resources?

STEPHANE BANCEL: No, actually, the piece that's very important about Moderna, is we have not slowed down the 20 plus other programs we have. We have very important medicines in cancer, cardiology, autoimmune disease, [INAUDIBLE] disease, and many more important first in class vaccines. Our CMV vaccines cytomegalovirus, number one cause of birth defects, is on its way to phase three this year.

Had a beautiful phase two neutralizing antibody data. It's a very complex product. There is no products on the market. And so we need to get these vaccines out there, because we need to protect women and the idea of bearing her child, because it's the number one cause of birth defect in this country.

ANJALEE KHEMLANI: Absolutely. Well, glad to hear it's all going well, and hopefully we'll have you back soon to discuss

even more milestones. Stephane Bancel, CEO of Moderna,
thank you so much for joining.

STEPHANE BANCEL: Thank you so much for having us.



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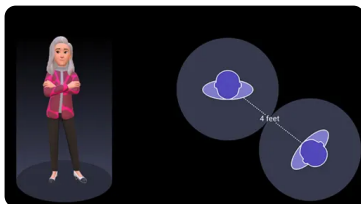


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EXHIBIT 18



Review

Nanomaterial Delivery Systems for mRNA Vaccines

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Mohamad Gabriel Alameh ³ and Drew Weissman ⁴

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Abstract: The recent success of mRNA vaccines in SARS-CoV-2 clinical trials is in part due to the development of lipid nanoparticle delivery systems that not only efficiently express the mRNA-encoded immunogen after intramuscular injection, but also play roles as adjuvants and in vaccine reactogenicity. We present an overview of mRNA delivery systems and then focus on the lipid nanoparticles used in the current SARS-CoV-2 vaccine clinical trials. The review concludes with an analysis of the determinants of the performance of lipid nanoparticles in mRNA vaccines.

Keywords: mRNA; lipid nanoparticle; ionizable lipid; vaccine; SARS-CoV-2



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1. Introduction

mRNA vaccines have been propelled to the center stage of the biotechnology and pharmaceutical industry by the COVID-19 pandemic. There are eight ongoing human trials for mRNA vaccines led by BioNTech/Pfizer, Moderna, CureVac, Sanofi/TranslateBio, Arcturus/Duke-NUS Medical School in Singapore, Imperial College London, Chulalongkorn University in Thailand, and Providence Therapeutics [1]. Remarkably, two of these trials have announced interim phase 3 trial results that report an efficacy providing a greater than 94% reduction in SARS-CoV-2 infection after 2 doses of 30 µg or 100 µg of an mRNA sequence encoding for a spike protein immunogen, delivered in a lipid nanoparticle [2,3]. The rapidity of vaccine development also exceeded expectations, with these results occurring only 10 months after the SARS-CoV-2 sequence was made publicly available. This success is a testament not only to the ability of the biotech and pharmaceutical industry to respond to an urgent and unmet global need, but also to the inherent capabilities of mRNA as a pharmaceutical modality, in this case a prophylactic vaccine. The purpose of this review is to overview the development of delivery systems for mRNA and then to summarize the preclinical and clinical findings of the SARS-CoV-2 mRNA vaccines and relate them to characteristics of the delivery system that contribute to their success. Several excellent reviews of mRNA delivery systems for vaccines and therapeutics that predate COVID-19 have been recently published [4–16].

Messenger RNA therapeutics have many advantages and several challenges compared to other pharmaceutical modalities, including small molecules, DNA, oligonucleotides, viral systems and proteins, including antibodies. The ability to mediate both stimulatory and inhibitory modes of action compared to oligonucleotides and most small molecule drug targets, and to express or replace defective proteins, expands the scope of potential indications for their use. Compared to DNA, mRNA only needs access to the cytoplasmic

ribosomal translation machinery rather than the nucleus and does not risk genomic integration. Compared to both proteins and viral systems, mRNA manufacturing is cell-free, faster, and the protein product bears native glycosylation and conformational properties. When combined with a lipid nanoparticle (LNP) delivery system, the nanostructural properties of the mRNA LNP also bear a resemblance to viral systems and circulating endogenous, lipid-containing chylomicrons in terms of their size, lipid envelope and, for viral systems, the internal genomic material that contributes to their application as delivery vehicles for vaccines and other therapeutics [17].

The challenges inherent to the mRNA platform are its intrinsic immunogenicity, susceptibility to enzymatic degradation, and almost negligible levels of cell uptake of naked mRNA. The innate immunogenicity of mRNA is due to the cellular detection of single- and double-stranded RNA by toll like receptors (TLRs)), helicase receptors, including retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and others [18,19], which then signal through NF- κ B and interferon (IFN) regulatory factors IRF3 and IRF7, which translocate to the nucleus to bind to the type I IFN gene promoter, inducing expression of type I IFNs (IFN- α and IFN- β), accompanied by proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), IL-6 and IL-12 [20]. The secreted interferons signal through their receptors and the JAK/STAT pathway in the same cell and adjacent cells to activate more than 300 IFN-stimulated genes, including the protein kinase PKR, as a general viral defense mechanism. Although this activation could be beneficial for mounting an immune response to mRNA vaccines, one immediate effect is the downregulation of translation through PKR phosphorylation of eIF2 α , which impairs eIF2 activity, inhibiting mRNA translation and thus the protein synthesis of the immunogen [21]. The primary means of abrogating this innate immune response is by substituting naturally occurring nucleosides such as 1-methylpseudouridine [22] and other nucleosides present in transfer and ribosomal RNA (but not typically in mRNA) into the mRNA sequence, which then renders it undetectable via these innate immune sensors [23,24]. This nucleoside-modified immunosilencing mRNA platform is the basis of the mRNA technologies that have recently shown >94% efficacy in the BioNTech/Pfizer and Moderna SARS-CoV-2 vaccine trials, building upon previous trials for other pathogens, which are described in detail below. A second approach pursued by CureVac is sequence engineering involving codon optimization and uridine depletion [25] since TLR7 and TLR8 primarily recognize GU-rich single-stranded RNA sequences [26]. The second challenge for mRNA therapeutics is its susceptibility to nucleases, exemplified by a half-life in serum <5 min [27]. Although chemical modifications of siRNA are highly successful in improving stability and lowering immunogenicity [28], to date, they have not been successful for mRNA due to the sensitivity of the translation machinery to these modifications [29]. The third challenge for mRNA is the lack of cell uptake of naked mRNA in most cell types [30], with the exception of immature dendritic cells [31]. These last two challenges are addressed by the incorporation of a nucleoside-modified or sequence-engineered mRNA into a delivery system that both protects the mRNA from enzymatic attack and facilitates cellular uptake. For example, incorporation into lipid nanoparticles protects the mRNA from enzymatic attack and enhances cell uptake and expression by up to 1000-fold compared to naked mRNA when administered in animal models [32,33].

Therapeutic mRNA is produced by in vitro transcription (IVT) from a plasmid DNA backbone to produce a full length message bearing a 5' cap, a 5' untranslated sequence (UTR), the open reading frame coding for the protein of interest, the 3'UTR and a polyA tail [4]. The natural eukaryotic 5' cap (cap0) is an inverted 7-methyl guanosine (m7G) linked to the first nucleotide of the mRNA by a 5' to 5' triphosphate. Cap0 protects endogenous mRNA from nuclease attack, is involved in nuclear export and binds to translation initiation factor 4 to start protein translation. Two additional 5' caps have been identified (cap1 and cap2) that contain additional methyl groups on the second or third ribonucleotide and are less immunogenic than cap0 (and therefore preferred) [34]. A commonly used current capping method involves a co-transcriptional capping process resulting in cap1,

which possesses high translation and low immunogenicity [35]. The 5'UTR is involved in translation initiation and can contain a Kozak sequence as well as an internal ribosomal entry site for cap-independent translation [36]. The open reading frame is followed by the 3'UTR, which influences mRNA stability and durability of protein expression. The polyA tail is encoded at around 100 residues and helps initiate translation and delay degradation. IVT production of mRNA needs to be followed by careful purification to remove DNA and double-stranded RNA contaminants, which are immunogenic [37,38]. The mRNAs described above can be nucleoside modified or sequence engineered without nucleoside modification, but are not capable of self-replication. Self-amplifying mRNA (samRNA) capable of replication are also being tested in clinical trials for SARS-CoV-2 and are longer ~10 kb sequences since they contain four additionally encoded nonstructural genes, including an RNA-dependent RNA polymerase, which result in self-replication inside cells but do not produce an infectious particle since they lack structural genes [39]. samRNAs cannot be nucleoside modified since these modifications interfere with self-amplification. Due to the amplification process, samRNAs typically use lower doses (1–10 µg) in the current COVID-19 clinical trials compared to 30–100 µg for non-amplifying mRNA. Interestingly, all of the above categories of mRNA vaccines are currently being tested in human clinical trials for SARS-CoV-2 and are summarized in Table 1. All mRNA delivery systems in these clinical trials are lipid nanoparticles. The exact composition of the Pfizer-BioNTech LNP [40] and Moderna LNP [41] have been publicly disclosed, while some others have not. The others are all most likely similar to the Alnylam Onpattro™ product (described further below) but with a proprietary ionizable lipid, as is the case for those that are disclosed. Although the specific ionizable lipid used may not be known in all cases, its general class can be understood from journal and patent publications and is indicated in Table 1.

Table 1. Current human trials for SARS-CoV-2 using mRNA lipid nanoparticles. All mRNA vaccines in SARS-CoV-2 clinical trials use a lipid nanoparticle for delivery. The identity and composition of each has not been publicly disclosed, so their probable class (shown below) is based on the available literature and patent citations.

Company	mRNA Type	Immunogen	mRNA Dose (µg)	Confirmed or Probable LNP Class	Publications
Moderna	nucleoside modified mRNA	membrane bound prefusion stabilized spike	100	Lipid H [42] confirmed in [41]	[43–46]
BioNTech Pfizer	nucleoside modified mRNA	membrane bound prefusion stabilized spike	30	Acuitas ALC-0315 [47] confirmed in [40]	[48–51]
CureVac	unmodified mRNA	membrane bound prefusion stabilized spike	12	Acuitas ALC-0315 [47]	[52,53]
TranslateBio Sanofi	unmodified mRNA	prefusion stabilized double mutant spike	7.5	ICE [54] or Cysteine [55]	[56]
Arcturus	self-amplifying mRNA	full length spike	1–10	Lipid 2,2 (8,8) 4C CH ₃ [57]	[58]
Imperial College	self-amplifying mRNA	membrane bound prefusion stabilized spike	1–10	Acuitas A9 [59]	[60]
Chulalongkorn	nucleoside modified mRNA	secreted wild type spike	Not available	Genevant CL1 [61]	NA

Prior to COVID-19, mRNA vaccines were used in preclinical and clinical studies for infectious diseases including influenza, zika, HIV, Ebola, rabies, chikungunya, malaria, genital herpes, toxoplasma gondii, and others. These studies are summarized in a number of excellent recent reviews [4,6,16,39].

2. Early Delivery Systems for mRNA Vaccines

Protamine, a mixture of small arginine-rich cationic proteins, has been used to form complexes with mRNA that improved transfection compared to naked mRNA [62]. Later, a mixture of free mRNA with protamine-complexed mRNA was introduced [63] since protamine-complexed mRNA partly inhibited protein expression [64]. Dynamic light scattering indicated that free mRNA have a size near 50 nm, while the protamine/mRNA

complexes were in the 250–350 nm range [63]. This approach was pursued by CureVac for a rabies vaccine candidate, CV7201, a lyophilized, temperature-stable non-modified mRNA composed of free and protamine-complexed mRNA encoding the rabies virus glycoprotein (RABV-G) [65]. In Balb/c mice, two doses of 10 µg and higher induced neutralizing titers greater than the WHO threshold of protection and administration of an 80 µg dose twice was protective against a lethal intracerebral challenge [66]. In a phase 1 human trial using doses 80–640 µg applied through intradermal and intramuscular routes, only a subgroup of participants who received three 80–400 µg doses using a particular injector device achieved the WHO neutralization titer threshold [67]. A serious adverse event (Bell's Palsy) occurred for one participant out of 101 at the highest dose and 5% of all participants experienced a solicited severe adverse event. The overall rate of all adverse events was high, with 97% experiencing injection site reactions and 78% a systemic adverse event. Given this suboptimal delivery with protamine complexed mRNA, CureVac adopted a lipid nanoparticle delivery system from Acuitas [47,68] and demonstrated greatly improved neutralizing titers at a 20-fold lower dose of 0.5 µg (vs. 10 µg for protamine complexed mRNA) in Balb/c mice and at a 10 µg dose in non-human primates [69]. Activation of T cell responses and the presence of IL-6 and TNF in the draining lymph nodes and injection sites indicated the role of the LNP in mediating the positive immune response. A clinical trial has been initiated (NCT03713086), with interim results expected to be reported in 2021.

A cationic nanoemulsion (CNE) was developed for mRNA delivery by combining the cationic lipid DOTAP with a commercial adjuvant (MF59) containing squalene, sorbitan trioleate, and polysorbate 80 in a citrate buffer of pH 6.5 [70]. The combined use of a self-amplifying mRNA encoding for respiratory syncytial virus glycoprotein (RSV-f) with an NP amine (from DOTAP) to phosphate ratio (of mRNA) of 7 resulted in an average 129-nm sized nanoparticle. One advantage of this approach is the ability to store CNE and mRNA separately and combine them only at the time of use. A 15-µg dose administered twice in Balb/c mice elicited neutralizing titers above that of an adjuvanted subunit vaccine. Detectable neutralization titers and T cell responses in non-human primates were achieved with two doses of 75 µg. Building on this concept, a separate group created a Nanostructured Lipid Carrier (NLC), which is a hybrid between a CNE and a lipid nanoparticle, consisting of a liquid oil phase, such as squalene, with a solid-phase lipid composed of a saturated triglyceride [71]. NLCs containing a self-amplifying mRNA encoding for a sika immunogen had a particle size of 40 nm and an NP ratio of 15 and were capable of generating protective neutralizing titers in C57BL/6 mice after a single injection of a dose as low as 0.1 µg or 0.01 µg.

3. Polymers for mRNA Delivery

Cationic polymers have been widely used for nucleic acid delivery for several decades, including for example poly(L-lysine), polyethylenimine (PEI), DEAE-dextran, poly(β-amino esters) (PBAE) and chitosan. In their simplest format, cationic polymers are mixed in excess with nucleic acid to form electrostatically bound cationic polyplexes. Although many polymers have been developed, they are not as advanced as lipid nanoparticles for nucleic acid delivery and the number of animal studies applying them successfully to vaccines is limited. PBAEs were co-formulated with polyethylene glycol (PEG)-lipids to form mRNA/PBAE/PEG-lipid nanoparticles that were capable of the functional delivery of mRNA to the lungs after intravenous administration in mice [72]. A biodegradable polymer, poly(amine-co-ester) (PACE) terpolymer, has been examined for mRNA delivery using erythropoietin as a reporter post-IV administration for gene delivery [73]. By controlling the molecular weight and end group chemistry, a 10 kDa member of the PACE family achieved the same in vitro transfection efficiency as TransIT, a potent but toxic colloiddally unstable and large-sized commercial reference. In vivo expression of EPO at 20 µg IV was fivefold more potent than TransIT. Hyperbranched poly (beta amino esters) (hPBAEs) were synthesized for mRNA delivery to the lung by inhalation. hPBAE mRNA polyplexes were 137 nm in size and were able to transfect 25% of the lung endothelium when nebulized and

inhaled in mice without evident toxicity and with expression levels 10-fold that of branched PEI [74]. A disulfide-linked poly(amido amine), pABOL, was synthesized at molecular weights ranging from 8 kDa to 167 kDa and was able to form polydisperse nanocomplexes near 100 nm in size [75]. In vivo luciferase expression of these polyplexes using a self-amplifying mRNA reporter was similar to that of PEI after intramuscular administration. When delivered to mice with a hemagglutinin (HA) influenza immunogen in a prime-boost design, neutralizing titers were highest for the low molecular weight 8 kDa pABOL and exceeded those of PEI. The 8 kDa pABOL delivering 1 µg HA of self-amplifying mRNA was also partly protective against a lethal influenza challenge, preventing death but not preventing significant weight loss. This pABOL system was considered for the delivery of a self-amplifying mRNA immunogen for SARS-CoV-2 by the group at Imperial College London; however, delivery of a SARS-CoV-2 immunogen with pABOL was 1000X less potent than delivery of the same immunogen with an optimized lipid nanoparticle from Acuitas [59]. In total, 1 µg of self-amplifying RNA in pABOL generated the same binding antibody and neutralization titers as 0.001 µg in an optimized lipid nanoparticle (Dr. Anna Blakney, personal communication). Many other polymer systems are capable of delivering mRNA in vitro or in vivo but remain to be tested in a vaccine context [76–84].

4. Development of Lipid Nanoparticles for the Current SARS-CoV-2 Clinical Trials

The earliest transfection reagent for mRNA was the quaternized cationic DOTAP combined with ionizable and fusogenic DOPE, adopted from DNA transfection [85] for the transfection of mRNA in numerous cell types [86]. Although effective in vitro, the permanently cationic quaternized ammonium group renders these large-sized lipoplexes rapidly cleared from circulation and from generally targeting lungs, as well as exhibiting toxicity. The forerunner of today's LNP was the stabilized plasmid–lipid particle (SPLP) that was formed by combining the fusogenic ionizable DOPE with a quaternized cationic lipid, DODAC, which electrostatically bound and encapsulated plasmid DNA, which was then coated with hydrophilic PEG to stabilize it in aqueous media and limit protein and cell interactions upon administration in vivo [87]. DOPE can be protonated in the endosome after cell uptake and, since it is cone-shaped, it can form an endosomolytic ion pair with endosomal phospholipids to facilitate endosomal release, a critical event for successful delivery [17]. The SPLP was then further developed as a Stabilized Nucleic Acid Lipid Particle (SNALP) containing siRNA that included four lipids: an ionizable rather than quaternized cationic lipid, a saturated bilayer forming quaternized zwitterionic lipid, DSPC, cholesterol and a PEG–lipid [88]. In addition to electrostatically binding to the nucleic acid, the ionizable lipid in the SNALPs played the role of the fusogenic lipid and became protonated in the endosome to form a membrane-destabilizing ion pair with an endosomal phospholipid. It is now known that DSPC helps form a stable bilayer underneath the PEG surface [89]. Cholesterol plays several roles, including filling gaps in the particle, limiting LNP–protein interactions and possibly promoting membrane fusion [90]. The ionizable lipid plays a central role by being neutral at physiological pH, thus eliminating any cationic charge in circulation, but becoming protonated in the endosome at pH ~6.5 to facilitate endosomal release. The development of the first siRNA product that was clinically approved in 2018 primarily focused on optimizing the ionizable lipid and, secondarily, the PEG–lipid and the ratios of the four lipids used in the LNP, as well as the LNP assembly and manufacturing procedure. An optimal number of unsaturated bonds in the C18 tail were found to be providing a dilinoleic acid tail linked by ethers to a dimethylamine headgroup [88], in accordance with the molecular shape hypothesis [12,91]. However, the introduction of a single linker to the dilinoleic acid tail, which had an optimized number of carbons from the dimethylamine head group to the linker, resulted in the pKa of the ionizable lipid in the LNP being near 6.4 for the ionizable lipid DLin-MC3-DMA [92,93]. The last step in the optimization was to tune the mole ratios of these lipids to 50/10/38.5/1.5 for MC3/DSPC/Cholesterol/PEG–lipid. Overall, this optimization process from DLin-DMA to DLin-MC3-DMA required more than 300 ionizable lipids to be screened in thousands of

formulations and resulted in a 200-fold increase in potency and a corresponding reduction in the effective dose in order to achieve durable suppression of the target gene >80% and a therapeutic window that permitted the clinical approval of Onpattro™ in 2018 [94,95]. This MC3 formulation developed for siRNA is the basis for the subsequent development of LNPs described below (Figure 1), which are now under emergency use after being approved for the delivery of SARS-CoV-2 mRNA vaccines.

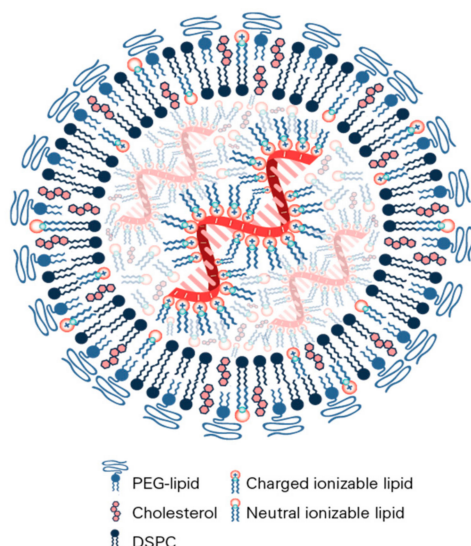


Figure 1. mRNA lipid nanoparticle structure. Recent studies using cryoelectron microscopy [96], small-angle neutron scattering and small-angle X-ray scattering [89] have shown that the mRNA Lipid nanoparticle includes low copy numbers of mRNA (1–10) and that the mRNA is bound by the ionizable lipid that occupies the central core of the LNP. The polyethylene glycol (PEG) lipid forms the surface of the lipid nanoparticle (LNP), along with DSPC, which is bilayer forming. Cholesterol and the ionizable lipid in charged and uncharged forms can be distributed throughout the LNP. Structural schematics of other delivery systems are available in a recent review [14].

Moderna carried out several preclinical [97–99] and clinical studies [97,100] using MC3 in the Onpattro formulation described above in order to deliver nucleoside-modified mRNA-encoded immunogens. MC3 was later identified [42,101] as the ionizable lipid in these studies comparing a new class of ionizable lipids to MC3. This new class includes Lipid H [42], which is the ionizable lipid SM-102 [41] in Moderna's SARS-CoV-2 product mRNA-1273 (Table 2). Using a nucleoside-modified mRNA-encoded immunogen for the Zika virus, the MC3 LNP was capable of protecting immunocompromised mice lacking type I and II interferon (IFN) signaling against a lethal challenge with one 10 µg dose or two 2 µg doses in a prime-boost design [99]. Similar results were obtained in immunocompetent mice pre-administered with an anti-ifnar1 blocking antibody to create a lethal model. In a series of influenza studies delivering nucleoside-modified mRNA-encoding hemagglutinin (HA) immunogens, the MC3 LNP delivered intradermally was capable of fully protecting mice against a lethal challenge with a single dose as low 0.4 µg, although post-challenge weight loss occurred even when up to 10 µg of a single dose was administered [97]. A single dose of 50 µg or 100 µg produced high HAI (hemagglutination inhibition assay) titers in ferrets, as did two doses of 200 or 400 µg in non-human primates. In a small number (23) of human subjects who received 100 µg doses, all had HAI titers >40 (the WHO correlate of protection) that were more than fourfold above the baseline at the beginning of the study. In a larger phase 1 trial using these same MC3 LNPs delivering two distinct nucleoside-modified mRNA-encoded HA immunogens, intramuscular injection of 100 µg of the H10N8 immunogen resulted in 100% of the 23 subjects having HAI titers >40 [100]. Although no life-threatening adverse events occurred, 3 of these 23 subjects experienced severe grade 3 adverse events. A planned 400 µg dose was discontinued after two of three

subjects experienced grade 3 adverse events, which met the study pause rules. At lower doses, the frequency and severity of adverse events diminished, although nearly every subject experienced at least one adverse event. These studies were promising, but also highlighted the relatively narrow therapeutic window to obtain protective immunizations at doses that do not cause a problematic number of adverse events. This is reminiscent of the narrow therapeutic window of the MC3 precursor, DLin-DMA, which needed an improved potency in order to lower the dose and still achieve efficacious gene knockdown.

Table 2. Ionizable lipids used in lipid nanoparticles. A key feature of the ionizable lipids used in lipid nanoparticles is that the pKa of the ionizable lipid in the LNP, as measured by the TNS dye-binding assay, should be in the range of 6–7. The theoretically calculated pKa of most of the ionizable groups is in the range of 8–9.5, as shown below on the nitrogen atoms, using commercial software that theoretically estimates these values in aqueous media. The 2–3 point drop in pKa from the theoretical value to the TNS value is due to the much higher energy of solvation of protons in the lipid phase, creating a pH increase of 2–3 points in the lipid compared to the aqueous phase, where pH is measured during the TNS assay [102].

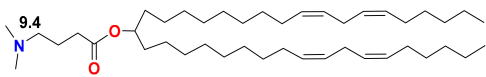
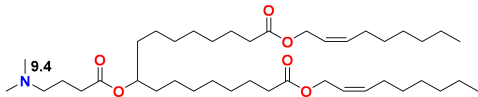
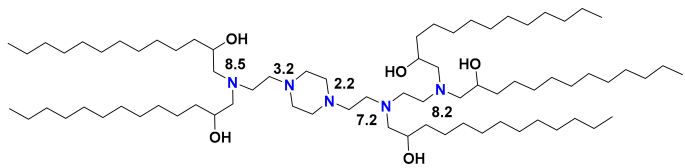
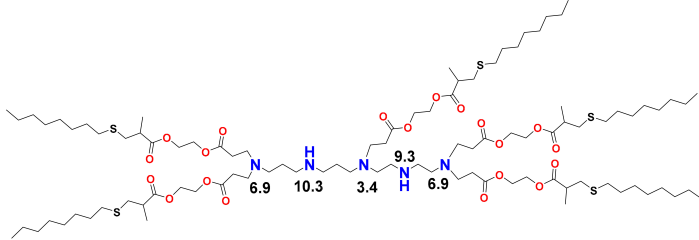
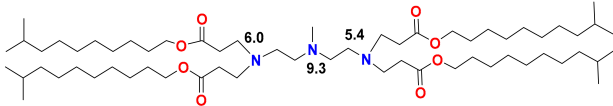
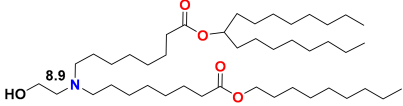
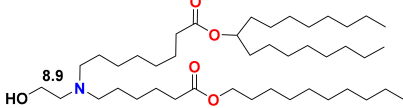
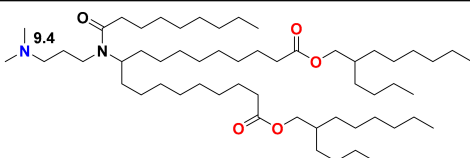
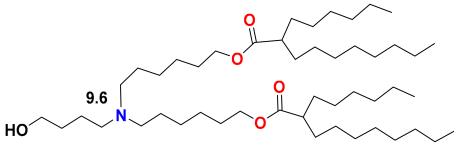
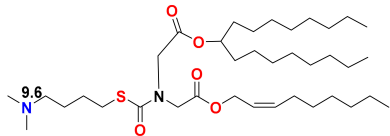
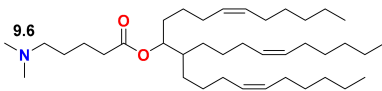
Name	Ionizable Lipid Structure and Theoretical pKas	TNS pKa
MC3 [92]		6.4
Lipid 319 [68]		6.38
C12-200 [103]		6.96
5A2-SC8 [104]		6.67
306Oi10 [105]		6.4
Moderna Lipid 5 [101]		6.56
Moderna Lipid H, SM-102 [42]		6.75

Table 2. Cont.

Name	Ionizable Lipid Structure and Theoretical pKas	TNS pKa
Acuitas A9 [59]		6.27
Acuitas ALC-0315 [47]		6.09
Arcturus Lipid 2,2 (8,8) 4C CH3 [57]		6.69
Genevant CL1[61]		NA

Since siRNA products require repeated dosing for chronic diseases, there was a concern that the slow degradability of the dilinoleic alkyl tail in MC3 would cause accumulation and potential toxicity with repeated dosing. A biodegradable version of MC3, Lipid 319 (Table 2), was generated by replacing one of the two double bonds in each alkyl chain with a primary ester that can be easily degraded by esterases *in vivo* [68]. A half-life of less than an hour in the liver was noted for Lipid 319, while it maintained a gene silencing efficiency in the liver that was similar to MC3. The degradation products were confirmed *in vivo*, as well as their secretion and the nontoxic nature of Lipid 319. This study of Lipid 319 is cited in the preclinical and clinical studies for SARS-CoV-2 as representing the Acuitas LNP class used in the BioNTech [49] and CureVac [53,69] products, although the Acuitas LNP delivering the self-amplifying RNA in the Imperial College London trial [60] is cited as having been contained in a more recent patent application [59], represented here by Lipid A9 from Acuitas (Table 2). Recently, the identity of the Acuitas ionizable lipid in BioNTech's approved BNT162b2 was disclosed [40] as ALC-0315 (Table 2). An important aspect of these LNPs is that they were developed by screening mRNA expression in the liver following IV administration and may not yet be fully optimized for the intramuscular administration of mRNA-based vaccines.

Moderna recently developed a new class of ionizable lipids to replace MC3, primarily due to the above-mentioned concerns related to the slow degradability of MC3, but also with the effort of increasing their potency by enabling greater branching than the dilinoleic MC3 alkyl tail [42,101]. This new class of lipids has an ethanolamine ionizable head group, connected to both a single saturated tail containing a primary degradable ester—like that of Maier 2013—and a second saturated tail that branches after seven carbons into two saturated C8 tails using a less degradable secondary ester, as in Lipid 5 [101] (Table 2), optimized for IV administration to the liver, and a similar Lipid H [42] or SM-102, found to be optimal for the intramuscular (IM) administration of vaccines. Increased branching is a common feature pursued by Acuitas, as Lipid A9 has a total of five branched chains [59] (Table 2) vs. three for the Moderna LNPs. Increased branching is believed to create an ionizable lipid with a more cone-shaped structure, so that—when paired with the anionic phospholipid in the endosome—a greater membrane-disrupting ability will occur, following the molecular shape hypothesis outlined several decades ago [12,91]. When administered IV, Lipid 5 was not detectable in the liver at 24 h, while MC3 was present

in the liver at 71% of its initial dose, verifying the degradability of Lipid 5. Lipid 5 was three-fold more potent than MC3 in mice for luciferase expression and five-fold more potent in non-human primates for hEPO after IV administration. These increases in potency were consistent with and possibly caused by an increase in endosomal release, with up to 15% of the mRNA in the cell being released from the endosome for Lipid 5 versus 2.5% for MC3, the latter being similar to that previously measured for MC3 using siRNA [106]. However, cell uptake in these endosomal release experiments was fourfold higher for MC3 vs. Lipid 5 so that absolute amounts of released mRNA in the cytoplasm were similar for these two LNPs. The same ionizable lipid library was examined in intramuscular administration for vaccines and was similarly found to be degradable and quickly eliminated due to the primary ester and generally to have a 3–6 fold increase in potency in terms of protein expression or immunogenicity compared to MC3 for an influenza nucleoside-modified mRNA encoded immunogen in mice, although immunogenicity in non-human primates was identical to MC3 at a 5 µg prime-boost dose [42]. Lipid H or SM-102 (Table 2) was identified as the optimal candidate and structurally only differs from Lipid 5, identified as optimal for IV administration, by a two-carbon displacement of the primary ester. The pKa of Lipid 5 LNP was 6.56, while that of the Lipid H LNP was 6.68, suggesting that a slight increase in pKa may be beneficial for IM vs. IV administration, although this difference is within the variability of the assay. Histological examination of muscle injection sites in rats indicated that Lipid H LNPs attracted less of a neutrophil- and macrophage-enriched inflammatory infiltrate compared to MC3, which may reduce injection site reactogenicity in human trials [42].

5. mRNA Lipid Nanoparticles in the Current SARS-CoV-2 Clinical Trials

5.1. BioNTech/Pfizer

Acuitas ALC-0315 (Table 2) combined with DSPC, cholesterol and a PEG-lipid is the delivery system in the SARS-CoV-2 trials of BioNTech [40]. CureVac and Imperial College London may also use ALC-0315, or possibly A9 (Table 2). BioNTech began developing its SARS-CoV-2 vaccine with four mRNA-encoded immunogens, two of which were nucleoside modified, one unmodified and one self-amplifying. Reports are available for the two nucleoside-modified mRNAs: BNT162b1 is a short ~1 kb sequence encoding the receptor-binding domain of the spike protein, modified by a foldon trimerization domain to increase immunogenicity by multivalent display. The longer 4.3 kb BNT162b2 encodes a diproline-stabilized, full-length, membrane-bound spike protein. BNT162b2 received EU and US emergency approval recently. In a preclinical study, binding antibodies and neutralization titers in mice were detectable after a single dose of 0.2, 1, and 5 µg of BNT162b2, increasing by an order of magnitude from the lowest to the highest dose and eliciting strong antigen-specific Th1 IFN γ and IL-2 responses in CD4 $^{+}$ and CD8 $^{+}$ splenocytes with very low levels of Th2 cytokines [49]. Draining lymph nodes also contained high numbers of germinal center B cells and elevated counts of CD4 $^{+}$ and CD8 $^{+}$ T follicular helper (Tfh) cells, which were previously identified as partly induced by the LNP alone in mRNA LNP vaccines [33]. In non-human primates, prime-boost doses of either 30 µg or 100 µg elicited binding antibody and neutralization titers that were more than 10 fold those of a human convalescent panel and a strongly Th1-biased T cell response that is believed to be important to protect against vaccine-associated enhanced respiratory disease [107]. In a limited number (6) of challenged rhesus macaques, two doses of 100 µg rendered undetectable viral titers in bronchoalveolar lavage and from nasal swabs. A phase 1 clinical trial for the smaller mRNA-encoded immunogen BNT162b1 planned 10, 30 and 100 µg doses on day 1 and day 21. The intermediate dose of 30 µg induced antibody binding and neutralization titers that were 30-fold and threefold higher than those of a human convalescent panel, respectively. The 100 µg dose was not administered for the boost due to the presence of severe injection site pain after the first dose. Injection site pain was reported by 100% of subjects with the 30 µg boost, but at mild or moderate severity. Following the second vaccination at the 30 µg dose, nearly all subjects experienced mild or

moderate systemic adverse events of fever, chills or fatigue. This trial also demonstrated strong Th1-biased T cell responses from peripheral blood mononuclear cells [50]. A phase 2 trial compared both BNT162b1 and BNT162b2 in groups of younger (18–55 y) and older (65–85 y) subjects [51]. Binding and neutralizing antibody titers were slightly lower in the older subjects, but still exceeded those in a convalescent panel. The severity of adverse reactions was also reduced in the older versus younger subjects. A significant reduction by ~twofold in the frequency of systemic adverse events (fever, chills, fatigue) was found in BNT162b2 versus BNT162b1. It was this increase in the tolerability of BNT162b2 that drove its selection for the phase 3 trial, where a 94% effectiveness was recently announced, since 162 COVID-19 cases occurred in the placebo arm, while only 8 cases were found in the vaccinated group that received two 30 µg doses of BNT162b2 [3].

5.2. Moderna

The nucleoside-modified mRNA encoded immunogen in Moderna's studies is a transmembrane-anchored diproline-stabilized prefusion spike with a native furin cleavage site and is delivered in an LNP that follows the prototype MC3 LNP, but replaces MC3 with Lipid H (SM-102) [41,42]. This mRNA LNP (mRNA-1273) induced neutralizing antibodies in several mouse species when injected at 1 and 21 days with a 1 µg dose, but not at a 0.1 µg dose [44]. The T cell response appeared to be a balanced Th1/Th2 response and viral titers in mice lungs and nasal turbinates in a mouse-adapted virus challenge model were reduced to baseline with two doses of 1 µg, but not with 0.1 µg. In rhesus macaques, 2 doses of 100 µg produced high binding and neutralizing titers and a Th1-biased response in peripheral blood that also involved a strong Tfh response [45]. Titers and T cell responses were significantly lower with two 10 µg doses. Similarly, the 100 µg dose was capable of reducing viral titers in bronchoalveolar lavages and nasal swabs to baseline, while 10 µg only did so in the lungs. In a phase 1 study with 15 patients per group receiving 2 doses of 25, 100 or 250 µg, separated by 4 weeks, binding and neutralization titers were ~10-fold higher than convalescent for the 100 µg dose, and about equivalent to convalescent at 25 µg [46]. Solicited adverse events were reported by all subjects at the 100 µg and 250 µg doses and 3 of 14 in the 250 µg group reported severe adverse events and were discontinued. In a subsequent phase 1 study in older patients (56–71 y and above 71 y), the 25 µg and 100 µg doses were found to produce binding antibody titers above those of convalescent plasma, while neutralizing titers were equivalent at 100 µg, but lower than convalescent at 25 µg [43]. Most patients (~80%) still experienced adverse events after the second vaccination, even in the older age group. Analyses of peripheral blood showed a CD4 T cell response that was Th1 biased. The higher neutralization titers for the 100 µg dose vs. the 25 µg dose resulted in its selection for the phase 3 trial, where interim results announced a 94.5% efficacy with 90 cases of COVID-19 in the placebo group versus five in the vaccinated group [2]. An independent board conducted an interim analysis of Moderna's phase 3 trial and found that severe adverse events included fatigue in 9.7% of participants, muscle pain in 8.9%, joint pain in 5.2%, and headache in 4.5%, while, in the Pfizer/BioNTech phase 3 trial, the frequency was lower with fatigue at 3.8% and headache 2% [108].

5.3. CureVac

The CureVac mRNA LNP (CVnCoV) is a non-chemically modified, sequence-engineered mRNA encoding a diproline stabilized full-length S protein delivered in an Acuitas LNP, possibly using the ionizable lipid ALC-0315. The number of weeks between two doses was examined ranging, from 1 to 4 when using 2 µg doses in mice, where it was found that the longer intervals produced higher titers and T cell responses and a balanced Th1/Th2 response in Balb/c mice [53]. The second dose was required to produce neutralizing antibodies and two doses of 0.25 µg were insufficient to produce neutralizing antibodies. In Syrian golden hamsters, two 10 µg doses (but not 2 µg) were able to reduce viral titers in the lungs (but not nasal turbinates) to baseline. In a phase 1 clinical trial examining 2–12 µg doses, neutralizing titers reaching the levels of convalescent sera were only found at the

highest 12 µg dose, resulting in higher doses of 16 and 20 µg being included in the ongoing phase 2 trial [52]. All patients at the 12 µg dose experienced systemic adverse events after each dose, the majority being moderate and severe, while >80% experienced local injection site pain at the mild and moderate levels.

5.4. TranslateBio

Translate Bio uses a non-modified mRNA encoding a double mutant form of the diproline stabilized spike protein delivered in an LNP that is cited as being based on the ionizable lipid C12-200 [109], but may be a more recently synthesized candidate from the ICE- [110] or cysteine-based [55] ionizable lipid families. In Balb/c mice, two doses in the range of 0.2–10 µg resulted in binding and neutralization titers well above convalescent levels. In non-human primates 15, 45 and 135 µg doses all generated titers exceeding the human convalescent panel [56]. The immune response was also Th1 biased.

5.5. Arcturus

Arcturus uses a self-amplifying, full-length, unmodified mRNA encoding a pre-fusion SARS-CoV-2 full-length spike protein in an LNP that uses an ionizable lipid with a thioester to link the amine-bearing headgroup to lipid tails via two additional ester groups. Two possible ionizable lipids in this family are Lipid 10a (in Table 4 of [111]) or Lipid 2,2 (8,8) 4C CH₃ (on p. 33 of [57]) (Table 2). The latter has three branches, resembling the Moderna Lipid H, but with a degradable thioester linked to the headgroup. A feature of self-amplifying mRNA was observed where luciferase reporter expression was maintained at a fairly constant level beyond one week of IM administration, while conventional mRNA expression fell quickly [58]. The vaccination alone surprisingly produced weight loss and increased clinical scores in C57BL/6 mice. Only a single dose at 2 µg or 10 µg (but not 0.2 µg) in mice was required to reach neutralization titers above 100 in a Th1-biased response with high levels of antigen-specific T cell responses. A single dose of 2 µg or 10 µg was also 100% protective in the K18-hACE2 lethal mouse challenge model, generating 100% survival with no weight loss and a reduction in lung and brain viral titers to baseline. Arcturus has completed a phase 1 clinical trial with doses from 1–10 µg and has chosen 7.5 µg for its phase 3 trial [112].

5.6. Imperial College London

Imperial College London uses a self-amplifying mRNA-encoded prefusion-stabilized spike protein delivered in an Acuitas LNP, which is described in the patent [59] represented by Lipid A9 [60] (Table 2). Remarkably high and dose-dependent antibody and neutralizing titers were obtained after two injections of doses in the range 0.01 µg to 10 µg in Balb/c mice. The response was strongly Th1 biased and the 10 and 1 µg doses produced threefold higher antigen-specific splenocyte responses compared to the lower 0.1 and 0.01 µg doses. A phase 1 clinical trial is about to start for this vaccine.

5.7. Chulalongkorn University, University of Pennsylvania

Chulalongkorn University, in collaboration with the University of Pennsylvania, is developing a native spike immunogen nucleoside-modified mRNA LNP using a Genevant LNP, likely CL1 Lipid [61]. They aim to begin phase 1 clinical trials in Q1 of 2021 and begin distribution of the vaccine in Q4 of 2021 to Thailand and seven surrounding low to moderate income countries.

5.8. Providence Therapeutics

Providence therapeutics was granted a Health Canada notice of authorization to pursue human clinical trials for the PTX-COVID-19B mRNA LNP vaccine [113]. Preclinical studies of three mRNA candidates encoding the receptor-binding domain, the full-length spike with or without a mutation in the furin cleavage site, were administered at a dose of 20 µg in C57BL6 mice following a prime-boost regimen [114]. Preclinical data using an undisclosed lipid from Genevant, possibly similar to CL1 In Table 2, showed robust neutralization titers for the full length and the furin-mutated payloads, reminiscent of the data observed in [115]. Phase 1 clinical trials are scheduled to begin in Q1 of 2021, with manufacturing and distribution of the vaccine—pending regulatory approval—in the same year.

5.9. Storage and Distribution

Most RNA LNPs made in the laboratory are stable at 4 °C for several days, but then exhibit size increases and a gradual loss of bioactivity, such as luciferase expression [116]. A size increase over time from LNP aggregation has been commonly observed in previous siRNA LNP formulations [117]. In order to stabilize mRNA LNP vaccines for storage and distribution, a frozen format has been required to date. The Moderna COVID-19 vaccine needs to be stored from −25 °C to −15 °C, but is also stable between 2 °C and 8 °C for up to 30 days and between 8 °C and 25 °C for up to 12 h [118]. The Pfizer/BioNTech COVID-19 vaccine needs to be stored from −80 °C to −60 °C and then thawed and stored from 2 °C to 8 °C for up to 5 days prior to dilution with saline before injection [119]. The dry ice temperatures required for the Pfizer vaccine are more difficult to achieve during distribution and storage than the regular freezer temperature required by the Moderna vaccine. The reasons behind these temperature differences are not obvious since both vaccines contain similar high concentrations of sucrose as a cryoprotectant. The Moderna mRNA LNPs are frozen in two buffers, Tris and acetate [41], while the Pfizer/BioNTech vaccine only uses a phosphate buffer [40]. Phosphate buffers are known to be suboptimal for freezing due to their propensity to precipitate and cause abrupt pH changes upon the onset of ice crystallization [120,121]. Lyophilization has been challenging for mRNA LNPs [116]. However, Arcturus has stated that their COVID-19 mRNA vaccine is stable in a lyophilized format, which would presumably greatly simplify distribution, although the temperature stability of this lyophilized formulation has not yet been disclosed [122].

6. Lipidoid Nanoparticles

A number of lipid-like entities, termed lipidoids, were initially developed for siRNA delivery and subsequently used for mRNA delivery. One example is C12-200 (Table 2), which was selected from a large lipidoid family due to its high efficiency in hepatocyte gene silencing via IV administration [123]. For efficient liver-directed gene silencing, C12-200 was combined with the same lipids as the MC3 Onpattro prototype, namely 50% ionizable lipid, 10% DSPC, 38.5% cholesterol and 1.5% PEG-lipid. A later study found that the C12-200 delivery efficiency for mRNA to the same liver target could be increased sevenfold by reducing the percentage of ionizable lipid to 35%, but increasing the weight ratio of ionizable lipid to nucleic acid from 5 to 10 and replacing DSPC with the fusogenic unsaturated DOPE [103]. Interestingly, this optimized formulation increased mRNA expression sevenfold, but did not change the silencing efficiency for siRNA. C12-200, in this formulation, has also been studied for mRNA-mediated protein replacement therapy in mice and nonhuman primates [124], but was seen to generate a strong inflammatory response by histology when injected subcutaneously [109]. C12-200 is a small molecule dendrimer with five alkyl chains and five nitrogen atoms, three of which appear to be protonatable, according to ionization analyses that can be performed with commercial software such as ACDLabs Percepta (Table 2). Another dendrimer lipidoid, 5A2-SC8, was identified for high siRNA delivery efficiency to the liver in a separate screening process, and also has five nitrogen atoms and five short alkyl chains [125] (Table 2). The 5A2-SC8 lipidoid

had poor efficiency for mRNA delivery unless its formulation parameters were similarly changed by lowering the ionizable lipid mole fraction to 24%, using DOPE instead of DSPC, and increasing the other lipid proportions, but, at the same time, increasing the weight ratio of 5A2-SC8 to mRNA to 20 [104]. These formulation changes appear to be needed for these dendrimer-type lipidoids to be effective mRNA delivery vehicles, possibly since they have multiprotic head groups and a dendrimer structure. Another very high molecular weight modified dendrimer was used to deliver self-amplifying mRNA encoding immunogens for influenza, Ebola and toxoplasma gondii and was shown to be protective against all three pathogens in mice after a single, very high dose of 40 µg or prime-boost 4 µg injections, which is also a high dose for replicating RNA [126]. An interesting recent finding for a series of lipidoids was that an additional single carbon branch at the terminus of each of the four alkyl chains of this small, three-nitrogen dendrimer increased the potency of liver expression more than 10-fold compared to other lipidoids in this class [105]. There was no correlation of this increased potency with the LNP pKa, but there was a correlation with the absolute fluorescence of the TNS dye at pH 5, which indicates that the amplitude of protonation in the endosome correlates to mRNA expression, presumably by facilitating endosomal release. The additional carbon branch could also be expected to produce a more cone-shaped structure and thereby more membrane disruption according to the molecular shape hypothesis [12,91].

7. Intranasal Delivery of mRNA Lipid Nanoparticles

For mRNA vaccines, the vast majority of studies and all current clinical trials have used intramuscular administration, while intradermal administration has also been studied, usually in parallel with the intramuscular route. Although not highly developed to date, intranasal administration of vaccines presents advantages such as the activation of mucosal immunity, which is very relevant for respiratory pathogens, and a reduced reliance on needle-based immunizations. The MC3 LNP has been used to deliver a 4.5 kb nucleoside-modified sequence encoding the cystic fibrosis transmembrane conductance regulator (CFTR) to mice [127]. A luciferase reporter was successfully expressed in the lungs by pipetting a 12 µg dose into the nostrils for spontaneous inhalation. Then, in a transgenic CFTR knockout mouse, application of CFTR mRNA LNPs restored CFTR-mediated chloride secretion to conductive airway epithelia for at least 14 days. MC3 LNPs were used again in a subsequent study of delivery to the nasal epithelium by using a luciferase reporter. Here, the use of a nebulizer to create an aerosol using the LNPs was examined; however, aerosolization resulted in LNP aggregation, doubling their size to 170 nm and resulting in a loss of transfection activity in vitro [128]. As a result, the researchers decided to instill the LNPs into the nostrils and found the luciferase reporter mainly expressed in nasal epithelia, with some additional transfection in lung epithelia. This study highlighted the delivery challenges of obtaining uniform and high levels of mRNA transfection in nasal and lung epithelia. Intranasal delivery of mRNA LNPs was also achieved using the older DOTAP/cholesterol/PEG-lipid system combined with protamine to encapsulate non-modified mRNA-expressing cytokeratin 19 in order to provoke a cellular immune response and slow tumor growth in a Lewis lung cancer xenograft model in mice [129]. These LNPs were large, 170 nm in size, and cationic, with 10 mV zeta potential and the ability to transfect 30% of DC2.4 dendritic cells in vitro. Once the xenograft tumor was established, 10 µg of cytokeratin 14-encoding mRNA LNPs was intranasally instilled in 100 µL PBS once per week for 3 weeks, resulting in a very significant reduction in tumor volume growth compared to the PBS control. A nucleoside-modified mRNA encoding the influenza antigen H3N2-HA was delivered in another study using DOTAP/DOPE/PEG-lipid LNPs, as well as in the same LNP-bearing mannose as a ligand to facilitate uptake by macrophages and dendritic cells [130]. These LNPs were also large, at 200 nm, positively charged, at 15 mV zeta potential, and able to express luciferase in the lungs following intranasal instillation of a 12 µg dose. Two 12 µg doses of the H3N2-HA LNPs were instilled intranasally at weeks 0 and 3 in C57BL/6 mice that were subsequently challenged with a

lethal dose of H1N1. Both LNPs containing the mRNA-encoded immunogen were capable of complete protection, while the mannose-coated LNP appeared more able to also block weight loss. Intranasal administration of LNPs appears feasible, although the doses were higher than those reported for intramuscular administration and the method of installation or aerosolization still requires further development.

8. Delivery of mRNA LNPs Encoding Antibodies

More than 70 monoclonal antibodies (mAbs) are currently on the market, with global sales of 125 billion USD. The possibility of using mRNA-encoded antibodies may bring some advantages, including endogenous protein synthesis benefiting from native post-translation modifications and a simplified manufacturing method that does not require cell culture and extensive purification and characterization of the protein product [8]. The feasibility of delivering mRNA-encoded mAbs for passive immunization was shown by the encapsulation of purified nucleoside-modified mRNAs encoding the light and heavy chains of VRC01, a broadly neutralizing antibody against HIV-1, into Acuitas LNPs [131]. Balb/c mice receiving a 30 µg dose IV that would target hepatocytes expressed the mAbs for more than a week, with serum levels reaching 150 µg/mL, which was higher than that obtained by direct injection of 600 µg of the mAb, with weekly injections capable of maintaining a constant serum level above 40 µg/mL. Both a 30 µg and a 15 µg injection of the mRNA LNP could protect CD34-NSG humanized mice from an HIV-1 challenge given 24 h later, as indicated by analyses of serum for viral RNA copies 2 weeks post challenge. The feasibility of therapeutic non-modified mRNA-encoded antibodies was confirmed in a study by CureVac, also using Acuitas LNPs [25], where an IgG mAb with broad neutralization ability for a variety of rabies strains was chosen, as well as a heavy chain-only Vh domain-based (VHH) neutralizing agent against the botulinum toxin [132]. An mRNA-encoded rituximab, targeting CD20, the gold standard for treating non-Hodgkin's lymphoma, was also produced. The animal studies here used an Acuitas LNP that targeted hepatocytes by IV administration. A single administration of 40 µg in mice produced serum levels of IgG just above 10 µg/mL, which gradually declined to 1 µg/mL after 1 month. The same dose of the VHH single-domain neutralizing agent produced 10-fold higher levels, but with a much shorter half-life of several days due to the absence of the Fc region. Single IV administration of 40 µg in mice was also able to entirely protect mice when administered either 1 day before or 2 h after a lethal challenge of the rabies virus. Similarly, a 40 µg dose 6 h after a lethal botulinum toxin challenge entirely protected the animals. A third challenge model, where Raji-luc2 B-cell lymphoma cells were engrafted intravenously and allowed to grow for 4 days and then 10 or 50 µg of mRNA-encoded rituximab in the Acuitas LNP was administered five times over 18 days, resulted in all animals surviving this lethal tumor challenge and the 50 µg dose was able to entirely abrogate tumor growth.

Bispecific antibodies that recruit T cells to tumor cells were also encoded in modified mRNA constructs and delivered in vivo using a commercial transfection reagent, TransIT, which is not as efficient as current LNPs for liver delivery [133]. The mRNA construct could sustain circulating and bioactive bispecific antibodies for more than 6 days, while the same 5 µg dose of the protein-bispecific antibody was reduced to near baseline after one day. A second study was also carried out using bispecific antibodies in the VHH format, where one VHH that binds the conserved influenza A matrix protein 2 ectodomain (M2e) was genetically linked to a second VHH that specifically binds to the mouse Fcγ receptor IV (FcγRIV) in order to recruit innate immune cells expressing FcγRIV to influenza infected cells expressing M2e [134]. These nucleoside-modified mRNA constructs were delivered using DOTAP/cholesterol LNPs by intratracheal instillation into the mouse lung and, 4 h later, challenged with a lethal influenza virus dose. Most of the mice (80%) were protected from the lethal dose, although they did experience significant weight loss and the DOTAP/cholesterol mRNA nanoparticles resulted in a temporary influx of granulocytes in the lungs, combined with an increase in serum IL-6 cytokine levels. Finally, a potent

neutralizing antibody identified in the B cells of a survivor of chikungunya infection was encoded in a nucleoside-modified mRNA construct delivered in an LNP possibly containing MC3 or Lipid 5 [135]. Protection against viral challenge administrated 24 h pre-infusion in mice was achieved at 0.5 mg/kg (10 µg) IV for the mRNA-encoded mAb, while 2 mg/kg of the protein mAb was needed. Therapeutic protection by infusion at 4 h post infection was obtained at very high doses of 10 mg/kg (200 µg) in mice. Non-human primate studies found that very high doses up to 3 mg/kg (9 mg) produced minimal transient toxicity involving splenic enlargement and increased CCL2 serum levels, and the antibody was detectable for several months post infusion. Based on these results, Moderna initiated a phase 1 human trial and announced positive results where infusions of 0.1 and 0.3 mg/kg were well tolerated and resulted in serum levels of the mAb in the 1–14 µg/mL range that are expected to be protective against chikungunya virus for up to 16 weeks after a single dose [136].

9. Assembly and Structure of Lipid Nanoparticles

The current methods of mRNA lipid nanoparticle production utilize microfluidic or T-junction mixing to rapidly combine an ethanol phase containing the hydrophobic lipids and an aqueous phase that contains the mRNA in a buffer, such as acetic acid, at pH 4 (Figure 2). Prior methods, such as thin film hydration and ethanol injection, are generally not used since they result in heterogeneous larger-sized nanoparticles with lower mRNA encapsulation efficiency, which are difficult to scale up [95]. Microfluidic mixing has the advantage of being able to mix very small volumes of lipids in ethanol with mRNA in aqueous solutions (tens of µL) so that the screening of many components and formulation parameters is possible. T-mixing, on the other hand, is the general method of choice for the commercial production of large batches of mRNA LNPs, such as those in current clinical trials. A recent publication demonstrated that both methods result in LNPs of similar sizes and morphologies [96]. The rapid mixing of the two solutions is key in order to limit the resultant particle size to <100 nm, thus obviating the need for the size reduction methods (extrusion, sonication) required by other production methods [137]. The assembly and formation of the LNPs from these solutions is driven by both hydrophobic and electrostatic forces, as depicted in Figure 2. The four lipids (ionizable lipid, DSPC, cholesterol, PEG-lipid) are initially soluble in ethanol without any counterions present so that the ionizable lipid is unprotonated and electrically neutral (Figure 2A). One volume of the lipid-containing ethanol solution is typically mixed with three volumes of mRNA in a pH = 4 aqueous acetate buffer so that when the lipids contact the aqueous buffer they become insoluble in a 3:1 water/ethanol solvent and the ionizable lipid becomes protonated and positively charged, which then drives it to electrostatically bind to the negatively charged phosphate backbone of the mRNA (Figure 2B), while the lipids become insoluble, forming a lipid particle encapsulating the mRNA in a primarily aqueous suspension. A key component in this process is the PEG-lipid, since the PEG chain is hydrophilic and thereby coats the particle and also determines its final thermodynamically stable size. By changing the mole fraction of PEG, the LNP size can be predictably controlled, for example, from 100 nm at a 0.5% mole fraction to 43 nm at a 3% mole fraction of PEG-lipid [89]. A recent critically important observation was that LNP structure and size continue to evolve post-mixing when the mRNA LNP suspension is either diluted in aqueous buffer or dialyzed against an aqueous buffer to both raise the pH and eliminate ethanol [96]. The initial mixing of aqueous and lipid phases produces a pH near 5.5, protonating the ionizable lipid, which has an LNP pKa of near 6.5 and allows mRNA binding and encapsulation (Figure 2B,C). Subsequent raising of the pH by dilution, dialysis or tangential flow filtration neutralizes the ionizable lipid until it is mainly uncharged at pH 7.4 (Figure 2D). As the ionizable lipid becomes neutral, it also becomes less soluble, resulting in the formation of larger hydrophobic lipid domains that drive the fusion process of the LNPs so that their size increases and the core of the LNP becomes an amorphous electron-dense phase, mainly containing the ionizable lipid bound to the mRNA. It was estimated that as many as 36 vesicles could fuse

to form just one final LNP during this process (Figure 2C,D). The fusion was demonstrated using FRET pairs and the role of the PEG-lipid was further seen to occur during this process since adding the PEG-lipid after mixing controlled the final LNP size in the same way as adding the PEG-lipid before mixing [138]. This study and another study using neutron scattering methods have also shown that DSPC forms a bilayer just underneath the peripheral PEG layer in the LNP, whose central core is primarily the ionizable lipid bound to mRNA (Figure 2D). Cholesterol is thought to be distributed throughout the LNP [89].

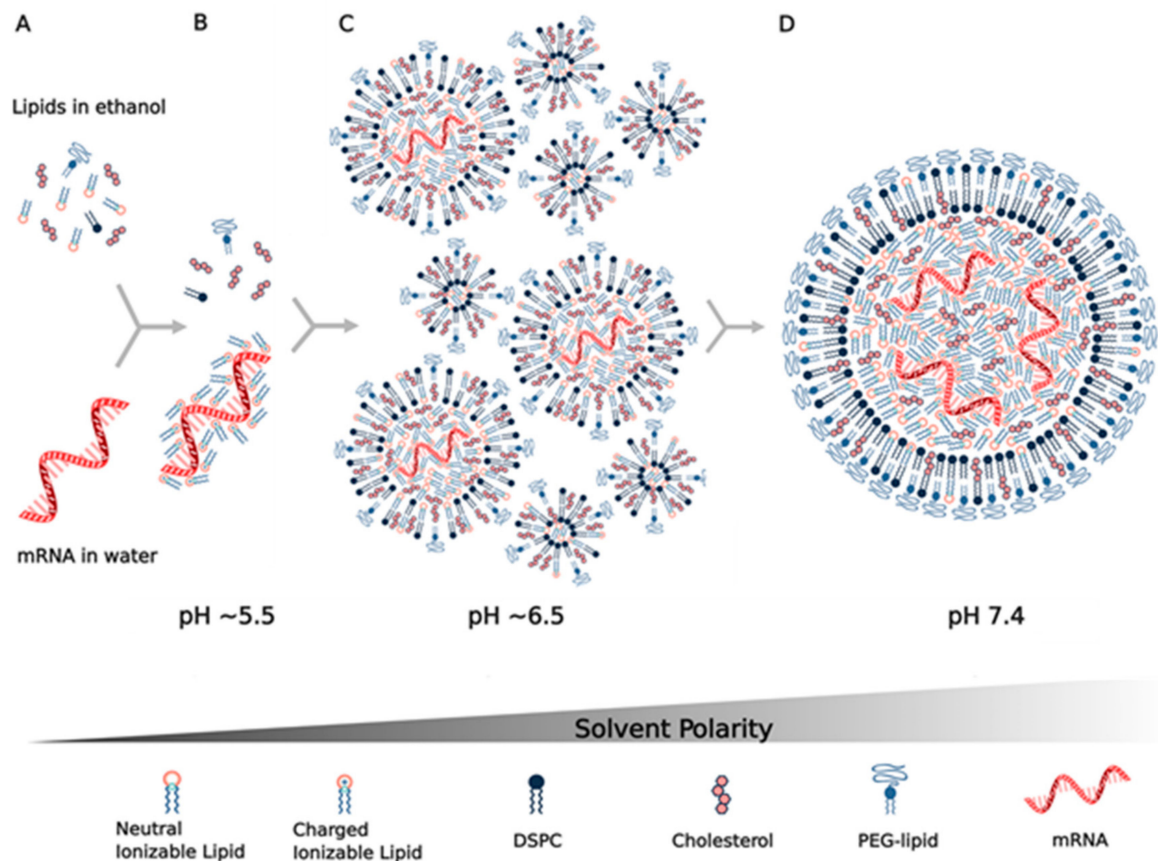


Figure 2. mRNA lipid nanoparticle assembly is achieved by (A) rapid mixing in a microfluidic or T-junction mixer of four lipids (ionizable lipid, DSPC, cholesterol, PEG-lipid) in ethanol with mRNA in an aqueous buffer near pH4. (B) When the ionizable lipid meets the aqueous phase, it becomes protonated at a pH ~5.5, which is intermediate between the pKa of the buffer and that of the ionizable lipid. (C) The ionizable lipid then electrostatically binds the anionic phosphate backbone of the mRNA while it experiences hydrophobicity in the aqueous phase, driving vesicle formation and mRNA encapsulation. (D) After initial vesicle formation, the pH is raised by dilution, dialysis or filtration, which results in the neutralization of the ionizable lipid, rendering it more hydrophobic and thereby driving vesicles to fuse and causing the further sequestration of the ionizable lipid with mRNA into the interior of the solid lipid nanoparticles. The PEG-lipid content stops the fusion process by providing the LNP with a hydrophilic exterior, determining its thermodynamically stable size, and the bilayer forming DSPC is present just underneath this PEG-lipid layer.

10. Determinants of Performance of mRNA Delivery Systems for Vaccines

The determinants of performance for mRNA delivery systems are multifactorial and interacting and include: (1) their potency or ability to deliver to the appropriate cell and efficiently release mRNA to the cytoplasmic translational machinery; (2) their adjuvanticity, which can boost the immune response; and (3) the minimization of any contribution to adverse events or toxicity that could arise from excessive inflammation at the injection site or systemic distribution and off-target expression.

10.1. Dose

The potency of mRNA delivery systems is most easily appreciated by the large range of doses that are currently being pursued in SARS-CoV-2 clinical trials, from 1 to 100 µg (Table 1). Doses in human trials are clearly grouped into the higher 30–100 µg doses for nucleoside-modified RNA (Moderna, BioNTech), lower 7.5–20 µg doses for unmodified RNA (CureVac, Translate Bio), and even lower 1–10 µg doses for self-amplifying RNA (Arcturus, Imperial College of London). Two factors are at play in determining these doses: the level of neutralizing antibody titers and T cell responses achieved versus convalescent plasma, and the frequency and severity of adverse events incurred at each dose. There appears to be a fairly narrow window of acceptance where the doses required to achieve protection are also close to generating an unacceptable frequency and severity of adverse events, as evidenced by the discontinuation of the highest doses tested in all phase 1 clinical trials. Both modified nucleoside constructs tested in the BioNTech phase 1 trials had high neutralizing titers versus convalescent plasma, while the larger construct encoding the membrane-bound full-length spike protein had a lower frequency and severity of adverse events, leading to its selection for the phase 3 study. Notably, dose is represented as mass, while the molar dose is dependent on the length of the construct and, furthermore, the amount of mRNA actually being translated is a small fraction of either, depending on the efficiency and targeting properties of the delivery system.

In animal studies of prophylactic mRNA vaccines for infectious diseases, the initial doses capable of producing neutralizing antibodies or protection against viral challenge were quite high in the 10–80 µg range for mice when using protamine, dendrimers and early cationic lipid systems (Table 3). When the more recent LNPs were subsequently used, the dose required for neutralization in mice was considerably reduced to near the 1 µg level when given twice, while for non-modified mRNA the dose appears to be lower, near 0.25 µg. The dose can be lower again for self-amplifying mRNA, such as 0.1 µg given twice or 2 µg given once. In larger animal models (hamster, ferret and non-human primate), fewer studies are available and the doses fall into a wide range of 5 µg to 200 µg with no apparent pattern. Interestingly, when using body surface area to convert human doses to animal doses, a 100 µg dose for a 60 kg human would be equivalent to a 15 µg dose in a 3 kg rhesus macaque and to a 0.4 µg dose in a 20 g mouse [139], numbers that approximate those of LNPs in Tables 1 and 3. The delivery system clearly plays an important role in determining the effective dose. There is a strong desire to improve delivery efficiency in order to reduce dose and maintain potency since this is expected to reduce adverse event frequency and severity by reducing the local reactions and off-target effects of the mRNA and of the delivery vehicle. Reducing the dose will also lower the amount of raw material needed and the cost associated with vaccinating each individual. In particular, the current COVID-19 pandemic has brought into focus some significant supply chain and production capacity limitations of mRNA LNP vaccines that could be improved with more efficient delivery systems.

Table 3. mRNA doses in in vivo prophylactic vaccination. The mRNA dose required to induce neutralizing antibody titers, or the dose that provides protection against viral challenge, is shown for different mRNA delivery systems and in different species. The advent of lipid nanoparticles (LNPs) for mRNA delivery reduced the required doses by ~10-fold compared to earlier delivery systems.

Delivery System	mRNA Type	Species	Dose	Readout	Reference
Naked mRNA	non-modified	mouse	80 µg twice	protection	[140]
Naked mRNA	self-amplifying	mouse	1.25 µg twice	protection	[140]
Protamine	non-modified	mouse	10 µg twice	neutralizing titers	[66]
Protamine	non-modified	mouse	80 µg twice	protection	[66]
Modified Dendrimer	self-amplifying	mouse	40 µg once or 4 µg twice	neutralizing titers	[126]
DOTAP/DOPE/PEG	nucleoside modified	mouse	12 µg twice intranasal	neutralizing titers and protection	[130]
Cationic Nanoemulsion	self-amplifying	mouse	15 µg twice	neutralizing titers	[70]
Nanostructured Lipid Carrier	self-amplifying	mouse	0.1 µg once	neutralizing titers	[71]
LNP (Acuitas)	non-modified	mouse	0.5 µg twice	neutralizing titer	[69]
LNP (MC3)	nucleoside-modified	mouse	10 µg once or 2 µg twice	protection	[99]
LNP (MC3)	nucleoside-modified	mouse	0.4 µg once	protection	[97]
LNP (Acuitas)	nucleoside-modified	mouse	0.5 µg once	protection	[141]
LNP (Acuitas)	nucleoside-modified	mouse	1 µg twice	neutralizing titers	[49]
LNP (Moderna)	nucleoside-modified	mouse	1 µg twice	neutralizing titers and protection	[45]
LNP (Acuitas)	non-modified	mouse	0.25 µg twice	neutralizing titers	[53]
LNP (Translate Bio)	non-modified	mouse	0.2 µg twice	neutralizing titers	[56]
LNP (Arcturus)	self-amplifying	mouse	2 µg once	neutralizing titers and protection	[58]
LNP (Acuitas)	self-amplifying	mouse	0.1 µg twice	neutralizing titers	[60]
LNP (Acuitas)	non-modified	Syrian Hamster	10 µg twice	protection	[53]
LNP (MC3)	nucleoside-modified	ferret	50 µg once	neutralizing titers	[97]
Cationic Nanoemulsion	self-amplifying	non-human primate	75 µg twice	neutralizing titers	[70]
LNP (MC3)	nucleoside-modified	non-human primate	200 µg twice	neutralizing titers	[97]
LNP (MC3 or Moderna Lipid H)	nucleoside-modified	non-human primate	5 µg twice	neutralizing titers	[42]
LNP (Acuitas)	nucleoside-modified	non-human primate	30 µg twice	neutralizing titers	[49]
LNP (Moderna)	nucleoside-modified	non-human primate	100 µg twice	neutralizing titers	[45]
LNP (Translate Bio)	non-modified	non-human primate	15 µg twice	neutralizing titers	[56]

10.2. Potency and Delivery Efficiency

There have been many studies that have attempted to identify structure–function relationships for LNP and other nucleic acid delivery systems. The most commonly cited feature of the LNP that determines its potency or delivery efficiency is its pKa. The pKa is the pH at which 50% of the ionizable lipid in the LNP is protonated. To date, the LNP pKa has only been measured with a dye-binding assay called TNS, which is negatively charged and experiences fluorescence enhancement upon binding a positively charged LNP [88]. Fluorescence measurement of LNPs incubated with TNS in buffers covering a wide range of pH values is used to deduce dye binding to surface charge and the pKa

estimated, where half of the maximal fluorescence is attained. It was well established that the MC3-based Onpattro LNP had an optimal pKa of 6.4 for silencing hepatocytes after IV administration [92]. There was a very sharp optimum in TNS pKa in the range of 6.2–6.8 for any LNP to effect hepatocyte silencing. An excellent model for explaining this pKa dependence was based on the ionizable lipid in the LNP being near neutral at pH 7.4 while, after internalization into a cell, the pH of the endosome will begin to drop as it evolves through the endolysosomal pathway, thereby progressively protonating the ionizable lipid, which will then bind to an anionic endogenous phospholipid of the endosome and disrupt its bilayer structure to release the mRNA into the cytoplasm for ribosomal loading [17]. Endosomal disruption requires an additional feature of the ionizable lipid, namely a cone-shaped morphology where the cross-section of the lipid tails is larger than that of its head group. This renders the ionizable lipid/endosomal phospholipid ion pair incompatible with a bilayer and more likely to form structures such as inverted hexagonal phases that can disrupt the endosomal membrane. This has been called the molecular shape hypothesis [91] and is the mechanism explaining why the introduction of one or two double bonds into a saturated C18 alkyl chain generates a more cone-shaped and less cylindrical morphology that is membrane disrupting and endosomolytic [88]. These two C18 linoleic acid tails, combined with an appropriately tuned pKa of the dimethylamine headgroup, are the defining features of the MC3 ionizable lipid. The ionizable lipids that have replaced MC3 for mRNA delivery conserve the pKa requirement, but pursue greater endosomolytic character by introducing more branching into the alkyl tails. Lipid H and Lipid 5 from Moderna, for example, have three alkyl tails, as does Lipid 2,2 (8,8) 4C CH3 from Arcturus, while Acuitas ALC-0315 has four and A9 has five alkyl tails (Table 2). This augmented cone-shaped morphology is presumably the reason why LNPs that incorporate these ionizable lipids are more efficient delivery vehicles with greater endosomal release.

Although LNP pKa and the molecular shape hypothesis are well established as contributing to LNP delivery efficiency, other factors are important as well, such as the stability of the PEG–lipid on the LNP surface, and the proportions of the four lipids in the ethanol solution, which ultimately determine the LNP ultrastructure. The PEG–lipid controls LNP size, as mentioned above, by providing a hydrophilic shell that limits vesicle fusion during assembly so that higher PEG–lipid concentrations produce smaller LNPs. For example, one study showed that varying the mole fraction of the PEG–lipid from 0.25% to 5% reduced the LNP size from 117 nm to 25 nm and that the optimal size for hepatocyte silencing was 78 nm, generated with 2.5% PEG–lipid [142]. Since the alkyl tail of the PEG–lipid had 14 carbons, it was not stably anchored to the LNP surface and was found to be gradually shed from the LNP in circulation, along with the shedding of the ionizable lipid MC3 and DSPC. This PEG shedding is thought to render the LNP transfection competent at some point, but, if too extreme, results in the rapid loss of the ionizable lipid and DSPC, which will negatively impact endosomal release. For example, by extending the alkyl tail to 18 carbons, the PEG–lipid did not shed, but was also not silenced in hepatocytes. On the other hand, adding higher concentrations of PEG to make smaller particles resulted in faster shedding, loss of the ionizable lipid and reduced silencing. The labile and dynamic nature of the LNP is currently only partly understood. Another study also found that an intermediate sized 64 nm diameter LNP made with 1.5% PEG–lipid was more efficient for mRNA delivery than a larger one at 100 nm (0.5% PEG–lipid), as well as a smaller LNP at 48 nm (3% PEG–lipid), similar to the study mentioned above [89]. However, by changing the mole ratios of the four lipids in order to conserve a calculated density of DSPC under the PEG layer of the LNP at the optimal value found in the 64 nm 1.5% PEG–lipid LNP, these authors were able to make larger 100 nm LNPs with a twofold increase in mRNA expression compared to the 64 nm-sized LNPs. Thus, in addition to the LNP pKa, ionizable lipid molecular shape and the dynamics of the PEG–lipid, more detailed features of the LNP ultrastructure and the state of each component are also important in determining potency.

10.3. Endosomal Release

Cell uptake and endosomal trafficking of siRNA-LNPs were studied in detail and are assumed to be similar to the uptake and endosomal trafficking of mRNA LNPs. With the MC3 LNP, a quantitative study using colloidal gold particle counting in electron microscopy showed that only 2% of siRNA that were in endosomes actually escaped from endosomes into the cytosol, resulting in a few thousand siRNA molecules per cell that were available for silencing [106]. This number was, however, in the same range as the estimated levels of functionally active siRNAs interacting with RISC per cell at therapeutically relevant concentrations. Thus, the vast majority of siRNA was destined for lysosomal degradation or recycling through multivesicular bodies (late endosomes) for release in the exosomes [143,144]. Increasing the endosomolytic behavior of LNPs is the central approach to improving delivery efficiency, mainly through pKa adjustment of the LNP and by increasing the cone-shaped morphology of the ionizable lipid. For the latter, Lipid H [42] and Lipid 5 [101], which contain three branches versus two in MC3, but with similar pKa, increased endosomal release fourfold compared to MC3. Endosomal release has not been reported for Acuitas ALC-0315; however, its hepatocyte silencing efficiency was 10-fold higher than MC3 [47], suggesting its more cone-shaped four-branch structure also had higher endosomal release. These newer generation ionizable lipids therefore appear to achieve a endosomal release, closer to 15% or higher compared to the 2–5% found for MC3 siRNA-LNPs. One of the challenges in this area is the lack of a reliable standardized endosomal release method that can be implemented broadly. Many methods have been developed, but are usually specific to only one lab group [42,101,145–149]. mRNA was also recently shown to undergo exocytosis in an amount that is similar to the amount released into the cytosol [150]. MC3 LNPs disassembled in late endosomes and NP 1 complexes of MC3 and the mRNA were repackaged into exosomes that were exported from the cell. These endo–exosomes maintained an mRNA delivery capacity that was similar to the original MC3 LNPs from which they were derived, but could traffic to different tissues and appeared to be less immune activating. The potential significance of this exosomal redistribution of mRNA delivered by LNPs remains to be explored.

10.4. Charge and Ligand Mediated Targeting

The early lipid nanoparticles using permanently charged cationic nonionizable lipids were large and, due to their permanent positive charge, were quickly opsonized and generally targeted the lung. The group at BioNTech reduced the amount of cationic DOTMA in DOTMA/DOPE mRNA LNPs until the net charge was negative due to an excess of anionic mRNA at NP ratios of less than one. Injecting these negatively charged and large 300 nm mRNA LNPs intravenously led to spleen targeting and mRNA expression in dendritic cells and they were able to mediate adaptive as well as type I IFN-mediated innate immune mechanisms for cancer immunotherapy [151]. Similarly, spleen-targeting mRNA LNPs were produced using the C12-200 prototype LNP, but replacing C12-200 with the small dendritic ionizable lipid Cf-Deg-Lin, which has four linoleic acid alkyl chains and four nitrogen atoms with a TNS pKa of 5.7. This very low pKa of the LNP would ensure that the ionizable lipid was not protonated until it reached a pH below 7, creating an LNP that would bear a net negative charge from the mRNA until quite late in the endosomal pathway and therefore similarly traffic to the spleen [152]. They found that the major cell population in the spleen to express the mRNA were B lymphocytes, where 7% of B lymphocytes were expressed the mRNA according to flow cytometric analyses. More recently, charge-mediated targeting was achieved using three different basic LNPs with MC3, C12-200, or 5A2-SC8 as ionizable lipids mixed in a certain mole fraction of a permanently cationic lipid (DOTAP) or a permanently anionic lipid (18PA) to endow the LNPs with a net positive, net negative or an intermediate near-neutral net charge [153]. Consistent with the above findings, highly positive LNPs targeted the lungs and highly negative LNPs targeted the spleen, while intermediate charge levels predominantly targeted the liver. Liver targeting

has been shown to depend on Apo-E binding to near-neutral liposomes or LNPs [154], which does not occur for negatively charged liposomes [155].

Notably, all of the above charge-mediated targeting studies have been done using IV administration and the routes typically used for vaccination, such as the intramuscular or intradermal routes, have not been examined. Most studies that analyze expression after intramuscular injection do, however, detect the systemic trafficking of mRNA LNPs, which are rapidly and strongly expressed in the liver, at the same time as they are expressed in muscle and draining lymph nodes [97,156,157]. These particular LNPs therefore seem to enter the vasculature and are subsequently expressed in liver hepatocytes due to passive ApoE-mediated targeting, which is not surprising since they were designed for hepatocyte targeting. This systemic distribution and expression of immunogens could, however, generate systemic cytokines, complement activation and lead to other potential undesirable effects that could amplify the frequency or severity of adverse events and/or impair immune response generation. Finally, only a limited number of studies have been carried out with ligand-mediated targeting of LNPs. Lung endothelial cell targeting was achieved by conjugating CD31 (PECAM) antibodies to the LNP and injecting intravascularly [158]. The liver hepatocyte-directed LNP then became largely redirected to the lung. A similar approach using a VCAM ligand successfully targeted LNPs to inflamed regions of the brain and alleviated TNF- α -induced brain edema [159]. Dendritic cells in vitro were also more efficiently transfected using a mannosylated liposome, which may be a strategy applicable to vaccination [160]. Higher throughput screening methods to identify ligands targeting specific cell types have also been developed and may be applicable for the targeting of specific dendritic cell subsets [161,162].

10.5. Adjuvanticity of the Lipid Nanoparticle

The lipid nanoparticle is known to have its own adjuvant activity. A study in mice at a 10 μ g dose and nonhuman primates at a 100 μ g dose of nucleoside-modified mRNA LNPs (from Acuitas) encoding various immunogens showed increased numbers of antigen-specific T follicular helper (Tfh) cells and germinal center B (GC B) cells compared to an inactivated virus [33]. Tfh cells drive immunoglobulin class switch, affinity maturation, and long-term B cell memory and plasma cells. An adjuvant property of the LNP itself was found when an FLuc mRNA LNP was co-administered with a protein subunit HA immunogen and increased germinal center B cell numbers fourfold, although the number of Tfh cells was not increased compared to the protein alone. The LNP thus appears to be amplifying GC B cell responses, in particular to a nucleoside-modified mRNA LNP. Another study using an asymmetric ionizable lipid from Merck investigated the use of LNPs as adjuvants for Hepatitis B protein subunit vaccines [163]. Co-administering LNPs with the protein subunit vaccine enhanced B cell responses to levels comparable to known vaccine adjuvants, including aluminum-based adjuvant, an oligonucleotide and a TLR4 agonist, 3-O-deacetylatedmonophosphoryl lipid A (MPL). The LNPs elicited potent antigen-specific CD4+ and CD8+ T cell responses and the Th1 vs. Th2 bias could be further influenced by the inclusion of additional adjuvants within the LNP. A follow-up study by this group using a Dengue virus immunogen found a similarly strong adjuvant activity in the LNP and that this activity depended on the presence of the ionizable lipid [164]. The lipid components in liposomes have also been previously recognized as having adjuvant activity in mucosal vaccines [165,166].

10.6. Injection Site Reactions, Safety, Tolerability, Reactogenicity of mRNA LNPs

A general safety study for MC3 nucleoside-modified mRNA LNPs expressing hEPO via IV administration to liver in rats and non-human primates found mild toxicological events up to 0.3 mg/kg, which is more than 10-fold the expected therapeutic dose [167]. The main findings in the rats were increased white blood cell counts, changes in the coagulation parameters at all doses, as well as liver injury. Non-human primates showed lymphocyte depletion accompanied by mild and reversible complement activation. These results

were in line with an earlier toxicological study of the same LNPs for siRNA delivery [168], where rat mortality was noted at 6 mg/kg, while the no observable adverse effect level (NOAEL) was determined to be 1 mg/kg. Above 3 mg/kg elevations to serum chemistry parameters (ALT, AST, and TBIL), hematuria, and microscopic findings in the liver (vacuolation, inflammatory cell infiltrate, fibrosis, hemorrhage, and hepatocellular necrosis), spleen (lymphoid atrophy and necrosis) and kidney (tubular degeneration/regeneration) were noted. Safety findings in patients included infusion-related reactions (15% of patients, presumably complement mediated) and transient elevations of pro-inflammatory cytokines. Notably, the above doses administered IV, such as 0.3 mg/kg, are more than 10-fold higher than those in the current SARS-CoV-2 clinical trials that use IM administration. Nonetheless, these lower doses in the current human trials still induce a high frequency and sometimes moderate severity of both local injection site reactions and systemic adverse events. Currently, there is a paucity of published animal studies regarding correlates of these human adverse events in animals.

An extensive rhesus macaque study looking at the injection sites and trafficking of mRNA expression was performed using the MC3 LNP, delivering a nucleoside-modified mRNA encoding the influenza immunogen H10 mRNA intramuscularly or intradermally at a 50 µg dose [98]. They found a rapid cell infiltrate to the injection site within 4–24 h that could be driven by the LNP alone and was mainly composed of neutrophils and monocytes. The main cell types expressing mRNA were multiple monocyte and dendritic cell subsets at the injection sites and in the draining lymph nodes. Priming of T cell responses was restricted to the draining lymph nodes and the LNP alone did not induce CD80 in antigen-presenting cells. Ongoing generation of vaccine-specific CD4+ T cells occurred only in the vaccine-draining lymph nodes, where detection of mRNA-encoded antigens peaked at 24 h, whereas the antibody responses were sustained for weeks. Results consistent with the above were also reported using a non-modified mRNA encoding rabies virus glycoprotein G (RABV-G), delivered in an Acuitas LNP to mice with 0.5–10 µg doses and to non-human primates at 10 µg and 100 µg doses [69]. They also found that the LNP alone mediated cytokine generation in the muscle injection site and draining lymph nodes, but recognized that systemic detection of IL6 could occur due to trafficking through the blood and expression in the liver. Injection site erythema and edema were noted in the non-human primates at both 10 µg and 100 µg doses. It is also interesting to note that the LNPs used in mRNA delivery systems have a size with the range of 10–100 nm, which is known to be optimal for uptake into lymphatics, and that pegylation of lipids improves retention in lymphatics [169] and can reduce complement activation [109]. Since the emergency use approval of the Pfizer/BioNTech vaccine, there has been several observed incidences of acute anaphylaxis corresponding to 1 case in 100,000 vaccinations, which is about 10-fold the rate seen with other vaccines [170]. One possible source of this anaphylaxis is the prevalence of anti-PEG antibodies in the general population, which could trigger anaphylaxis in a patient subset due to the use of the PEG-lipid in LNPs. PEG-mediated anaphylaxis has been noted, for example, in a clinical contrast agent [171] and in a liposomal formulation of doxorubicin [172]. Nonetheless, the doses administered for the current SARS-CoV-2 vaccines correspond to a total PEG dose that is at least 15-fold lower than that found in those products, which seems to diminish this possibility. Another possibility is that the reactions are anaphylactoid in nature, but are non-specific responses to inflammation and other factors. A clinical study is underway to further elucidate this issue [173].

11. Conclusions

The progress of mRNA therapeutics has been extraordinary over the past two decades, beginning with the identification of means to control mRNA innate immunogenicity using modified nucleosides and sequence engineering, and the application of mRNA in vaccines and other therapeutic indications. The adoption of the lipid nanoparticle prototype from that used in siRNA delivery led to an order of magnitude improvement in delivery efficiency compared to previous systems and is continually improving, mainly due to the

design of new classes of ionizable lipids. Many aspects of mRNA LNP structure, function, potency, targeting and biological features, such as adjuvanticity, remain to be explored in order to fully exploit the potential of this powerful and transformative therapeutic modality.

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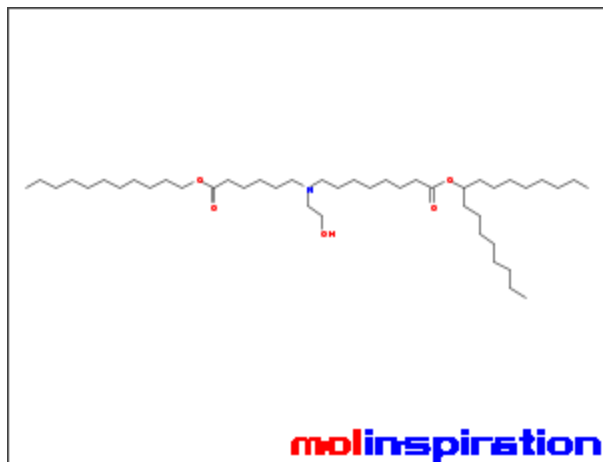
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EXHIBIT 19



Calculation of Molecular Properties

originalSMILES CCCCCCCCCCCCOC(=O)CCCCN(CCCCCCCC(=O)OC(CCCCCCCC)CCCCCCCC)CCO
 miSMILES: CCCCCCCCCCCCOC(=O)CCCCN(CCCCCCCC(=O)OC(CCCCCCCC)CCCCCCCC)CCO
 Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate



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miLogP	10.18
TPSA	76.08
natoms	50
MW	710.18
nON	6
nOHNH	1
nviolations	2
nrotb	43
volume	794.35

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